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Vol. 218 No. 4 OCTOBER, 1949 No. 931

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

OCTOBER, 1949

ORIGINAL ARTICLES

A STUDY OF FACTORS AFFECTING THE PROGNOSIS OF CEREBRAL VASCULAR ACCIDENT

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Except for a study by Brown[2], the problems pertinent to prognosis in cerebral vascular accidents have received only incidental attention. Although several authors[5,6,7,9,12,14] suggest factors which seem to influence the prognosis and a few of them discuss longevity in cerebral vascular accidents, none attempts to establish prognostic criteria. Such criteria, as vicarious adjuncts to the necessary clinical experience, appear to be needed urgently, especially as cerebral vascular accident is one of the commoner causes of death and incapacity. In view of this, it was decided to study the pattern of behavior manifested by a series of spontaneous acute cerebral vascular accidents, in order to appraise the formulation of prognostic standards.

Material Studied. The cases studied were all admissions to the Wisconsin General Hospital. All syndromes due directly to trauma, infection, neoplasia, hemorrhagic blood dyscrasias and congenital anomalies were excluded, leaving only the acute spontaneous cerebral vascular accidents. The diagnoses were carefully re-analysed in accordance with the work of Aring and Merritt[1] to segregate them into their groups of hemorrhage thrombosis and embolism.

In Table 1 are enumerated the criteria, derived by Aring and Merritt

TABLE 1.—CRITERIA FOR THE DIFFERENTIAL DIAGNOSIS OF CEREBRAL VASCULAR ACCIDENT

Sign	Hemorrhage	Thrombosis	Embolism
Syncope	+++	+	±
Cephalalgia, severe, sudden	+++	+	±
Emesis	+++	++	+
Convulsions	++	+	+
Coma	++	±	+
Bloody spinal fluid	+++	±	±
Raised spinal fluid pressure	+++	±	±
Nuchal rigidity	++	+	±
Signs progressive	++	±	±
Embolic disease	±	±	+++

+++ = Usual
++ = Frequent
+ = Infrequent
± = Rare

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from a clinico-pathologic study of 245 fatal cases of cerebral vascular accident, as we employ them to establish our differential diagnoses. Notwithstanding the usual clearcut differences, the distinction of the types is not always simple. There is no one clinical sign by itself which can decide the differential diagnosis. The types may so closely approximate one another and overlap that they are occasionally indistinguishable. In making a diagnosis, Aring and Merritt, and later Levy[8], stress the necessity of a careful analysis of the history, together with the results of the physical and neurological examinations and of the examination of the cerebrospinal fluid. They indicate that on this basis differentiation is possible in nearly 100% of cases. Of the 26 cases dying in our institution, autopsy permission including examination of the brain was obtained in 12. The autopsy substantiates our diagnosis in 11 of these (92%). We assume, therefore, that the criteria of these investigators, as we use them, obviate the diagnostic difficulties in the majority of our cases.

On the basis of a rigid selection, 107 cases are finally accepted as examples of primary acute cerebral vascular accident, with data adequate to our purposes. The significant information concerning age, sex, variation in blood pressure, abnormality of respiration and cerebrospinal fluid analysis is obtained from the protocols of each case. Insofar as the blood pressure is difficult to evaluate immediately subsequent to a cerebral accident, it was decided to use the highest pressure recorded during hospitalization, as has been done by other investigators. On the contrary, no attempt is made to localize the exact site of the cerebral lesion, because in acute cases such as ours the lability of neurological signs stultifies the value of anatomical localization[15]. In such cases as survived the initial attack, an attempt has been made to determine the occurrence of subsequent accidents, the longevity and the patient's state of health at the time of inquiry. This investigation reveals the subsequent histories of 65.4% of those who survived the first cerebral vascular accident, with details sufficient for our analysis.

Among the 107 selected cases of cerebral vascular accidents there are 75 cases of hemorrhage, 27 of thrombosis, and 5 of embolism, with an aggregate of 132 separate attacks. Fourteen patients (13%) have suffered more than one attack, ranging from 1 to 5 episodes. There are 26 fatalities on the initial attack, with 81 survivors, of whom 53 are traced adequately. Among those whom we traced, 33 are known to be alive at the time of the study. The relative proportions of hemorrhage, thrombosis and embolism in our series are similar to those of Aring and Merritt[1], although we believe that neither their nor our figures represent the true general incidence. In Courville's[4] series of 15,000 autopsies, there were 569 cases of cerebral thrombosis and 388 cases of cerebral hemorrhage; when these are so analysed as to exclude cases which are not primary, the ratio is still 497 to 208 in favor of thrombosis. An almost simultaneous clinical survey of 600 cases by Merritt[10] illustrated an incidence of 66% for thrombosis and 21% for hemorrhage. Some authors believe that the preponderance of hemorrhage in their autopsy series is because most cases of thrombosis recover to a sufficient extent to leave hospital. It is our experience, perhaps due to certain geographical peculiarities, that because they are milder, the thromboses are not sent to our institution, whereas the severer cases of hemorrhage are. Because of this our examples are weighted by the number of hemorrhages.

Results of Analysis. *Age.* The majority of cases in the present series occurred between the fourth and seventh decades, with the highest incidence in the sixth. The mean average is 56 years and approximates expectation. There are relatively few cases before 40 years of age; only 12 of our cases fall into the younger categories, with 10 of these in the fourth decade. The type of accident is not peculiar to any age. Our examples of embolism, however, are too few to permit inference concerning them and, because we have not included cases of cerebral vascular accident secondary to other disease, our representation of embolism may not correspond to the true incidence.

When the instances of cerebral hemorrhage are separated into fatalities and survivals, it emerges that, whereas the number of fatalities rises slightly with age, it is far less than proportionate to the increased incidence of such accidents (Fig. 1). The disparity between incidence and mortality percentage is most extreme at the age of greatest occurrence. It is furthermore apparent (Table 2) that the percentage mortality per age group increases as that group deviates from the age group of highest incidence. Such cerebral vascular accidents as occur prior to 40 and later than 60 years are more likely to be fatal than an attack occurring between these ages. That this applies to accidents in children is open to question, since but 2 of our cases were under 30 years of age.

TABLE 2.—THE AGE INCIDENCE OF CEREBRAL HEMORRHAGE AND THE PERCENT MORTALITY ACCORDING TO AGE IN 75 CASES

Age Group (years)	Number of Cases	Percent Incidence	Number Fatal	Percent Fatal
10-29	2	2.6	1	50.0
30-39	8	10.6	3	37.5
40-49	10	13.4	3	30.0
50-59	26	34.6	5	19.2
60-69	19	25.4	5	26.3
70-79	10	13.4	5	50.0
Total	75	100.0	22	29.2

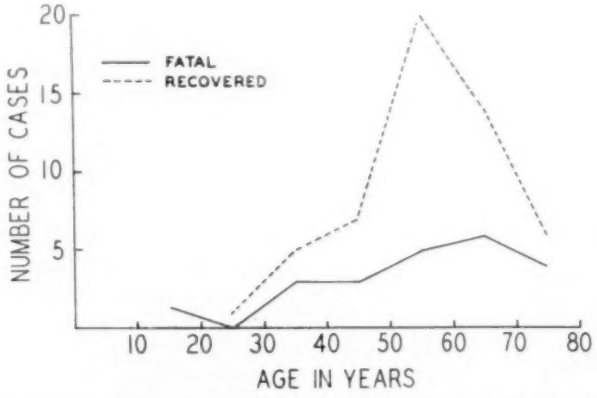

FIG. 1.—The divergence of incidence and mortality rate of cerebral hemorrhage with increasing age up to the age of 50 is demonstrable. The approximation of these is seen at the extremities of life.

The cases of thrombosis in the present series have a similar age distribution to those with hemorrhage. But the mortality rate on first attack is so low, 2 instances among 27 thromboses (7.5%) that the condition is a striking contrast to hemorrhage, in which the mortality was 29.2% in the first episode. It is deduced from this

that age is not so clearly a factor in deaths from cerebral thrombosis as it is in hemorrhage. Age, which assumes considerable importance in the latter type of accident, is of relatively slight significance in the thrombotic accidents; wherefore the accurate delimitation of these two types is of the utmost value.

Blood Pressure. The cases of cerebral hemorrhage after the initial attack are divided into fatalities and recoveries, and their blood pressure readings, both systolic and diastolic, are compared. It becomes apparent that until the systolic pressure is elevated above 190 mm. Hg., and the diastolic rises beyond 140, the mortality percentage is not appreciably affected in relation to blood pressure. With pressures above these readings a significant augmentation of mortality ensues (Tables 3 and 4), when

TABLE 3.—RELATIONSHIP OF MORTALITY PERCENTAGE AND SYSTOLIC BLOOD PRESSURE IN FIRST ATTACK OF CEREBRAL HEMORRHAGE

Systolic Pressure (mm. Hg.)	Number of Cases	Number Fatal	Percent Fatal	
100-139	20	3	15.0	
140-169	19	4	21.0	17.6
170-189	12	2	16.0	
190-260	24	13	54.1	54.1
Total	75	22	29.2	

TABLE 4.—RELATIONSHIP OF MORTALITY PERCENTAGE AND DIASTOLIC PRESSURE IN 75 CASES OF FIRST ATTACK OF CEREBRAL HEMORRHAGE

Diastolic Pressure (mm. Hg.)	Number of Cases	Number Fatal	Percent Fatal
60-99	31	8	25.8
100-139	35	8	22.8
140-190	9	6	66.0
Total	75	22	29.2

such pressures are found subsequent to the accident. Which reading, systolic or diastolic, is of greater value is still problematic, but from the present series it appears that, as an indicator, the systolic has a slight advantage as compared with the diastolic pressure.

The average blood pressure of the fatal cases is 197/115, and 75% of them have pressures above normal. It is pertinent that, among the fatal cases with normal pressures, 4 were affected by severe complicating diseases which significantly contributed to the mortality. With the exclusion of these cases the remainder have an average systolic pressure of 211 mm. Hg. and a diastolic of 122. On the other hand, the average pressures for the recovered cases are 168 mm. Hg. systolic and 102 diastolic. By treating the groups comparably and eliminating cases with severe complications, these distinctly lower pressures are not altered. Although the number of deaths by thrombosis following the first attack is too small for significant subdivision, it is noteworthy that the pressures in the 2 fatal instances have been normal. On the other hand, the mean average pressures for the entire group of thromboses are 174 mm. Hg. systolic and 105 diastolic, which figures approximate those found for the recovered cases of cerebral hemorrhage.

Superficially it would appear that considerable significance might be attached to these figures and that very high blood pressure may be a decisive factor. However, when statistically analysed by the method of Chi squares, the element of chance variation cannot be excluded rigidly. The deviation from the required result after the statistical treatment is small enough, nevertheless, to indicate that a more extended series may substantiate the suggested significance of the difference in pressures between the fatal and non-fatal groups.

Recurrence of Attacks. Consideration of the repetition of attacks in cerebral vascular accident entails 2 problems. One is that of the expected mortality in each succeeding episode, and the other concerns the probability of a subsequent attack. In cerebral hemor-

rhage (Table 5) the mortality after a first attack is 29.2%, after a second 30%, whereas succeeding third and fourth attacks have a 50% and 100% mortality respectively. The examples of third and fourth attacks are so few that these figures are not significant. But there is no difference between the mortality rates of first and second attacks. It is of further interest that the combined mortalities of the attacks other than the first represent 11% of all those patients surviving the first attack. Since the mortality of first and second attacks of hemorrhage is similar, the probability of a repetition gains added interest. Ten (18.8%) of the survivors of the initial cerebral hemorrhage developed one or more acute attacks. With this low probability of a succeeding event and the same mortality for such an occurrence, the hazard from this direction may be regarded as appreciable but not major. Since the incidence of the second attack is 18.8% and the mortality of such an episode is 30%, it may be deduced that the expectation of any survivor that he may die of such an occurrence is 5.6% or approximately 1 in 20. For cerebral thrombosis the mortality after the initial attack is very low (7.5%) and subsequent attacks in our series are too infrequent to allow further analysis, although this rarity of recurrence appears contrary to clinical experience in thrombosis.

TABLE 5.—THE RELATIONSHIP OF RECURRENT ATTACK AND PERCENTAGE OF MORTALITY IN 75 CASES OF CEREBRAL HEMORRHAGE, 27 OF THROMBOSIS AND 5 OF EMBOLISM

	Hemorrhages			Thromboses			Embolisms		
Attack	Cases	Number Fatal	Percent Fatal	Cases	Number Fatal	Percent Fatal	Cases	Number Fatal	Percent Fatal
1st	75	22	29.2	27	2	7.5	5	2	40
2nd	10	3	30.0	2	1	50	2	1	50
3rd	4	2	50.0	1	0	0	1	0	0
4th	1	1	100.0	1	1	100	1	0	100

Duration between Attacks. The average time between first and second attacks of cerebral hemorrhage is 46 months with a wide range of variation. In fatal cases of second episode the interval measures 12 months, whereas in non-fatal second attacks the interval is 76 months. This discrepancy is further substantiated by the fact that the average duration between second and third attacks is 2 months for the fatal and 10½ months for survivors. This may indicate that the mortality is inversely proportional to the length of time between attacks of hemorrhage; the sooner the recurrent attack ensues the more likely it is to be fatal. However, this is merely an indication which requires the confirmation of a larger series of cases.

Coma and Respirations. Two additional phenomena are found to bear upon prognosis; these are coma and abnormal respiration. Whereas the depth of coma is unrelated to the outcome of the cerebral vascular accident, the duration is of considerable importance. In the 22 fatal cerebral hemorrhages, the duration is several hours, and in 4 instances is stretched beyond 2 days. In the cases which recovered, such coma as was observed lasted no longer than 2 hours in any instance. On the other hand, all except 6 of the fatal cases (76.9%) have exhibited prolonged periods of abnormal respiration, particularly the Cheyne-Stokes phenomenon. The cases which recovered have manifested only transient episodes of abnormal respiration. In the fatal cases which have lacked res-

piratory abnormality, the period of survival time is 11.6 days, compared with 7.9 for the remainder who have manifested severe symptoms. Prolonged coma and protracted episodes of abnormal respiration may be said to emphasize the gravity of immediate prognosis.

Discussion. In his assessment of cases of cerebral vascular accident, the clinician is confronted with two problems of prognosis. One is the immediate prognosis of any case in its acute phase, an exceedingly difficult task; the other is the ultimate or "long term" prognosis, which is the outlook in such cases as recover from an attack. The immediate prognosis will in a large measure depend upon the type of accident; there is a 30% mortality in hemorrhage compared with a 7.5% mortality in thrombosis, whereas in cerebral embolism the future is colored by the associated disease responsible for the emboli. It is most important, therefore, to separate the conditions by an accurate diagnosis, since it so substantially affects the prognosis.

Among the features which may so characterize a cerebral vascular accident as to sway the prognosis, are the age of the patient, the duration of coma, the presence of atypical respiration and the height of the blood pressure. In our series there is strong evidence that the mortality varies with age, and that it is greatest at the extremes of life, least during the fifth and sixth decades. This would indicate that during these decades the prognosis is more favorable. Of the cases in our series which sustained coma and recovered, the duration did not exceed 2 hours. MacDonald[9] avers that coma lasting for longer than 48 hours is a very bad sign; to this our experience attests. Moreover, although brevity and absence of coma may not preclude a fatal outcome, they indicate a more favorable prognosis. On the other hand, the occurrence of atypical respiration, particularly if prolonged or of Cheyne-Stokes variety, is a sign of considerable gravity. All except 6 of our fatalities manifested this sign. Aring and Merritt[1] mention that Cheyne-Stokes and other forms of respiration are frequent in their series and that a practically constant finding in any type of accident is the uniform rise of temperature, pulse rate and respiratory rate several hours or days before death. With this our studies agree.

With regard to blood pressure, we tentatively regard a very high pressure as unfavorable. Although exact figures have limited value, a systolic pressure over 190 mm. Hg. and a diastolic over 140 suggest a poor prognosis. As was shown above, the statistical analysis fails to satisfy the requirements for complete exclusion of chance variation, but suggests a more extensive study. The height of the pressure may serve, therefore, as an indicative though not conclusive sign. Its value is enhanced by the behavior of the pressure in thrombosis, where it has been so low as to approximate that of non-fatal cases of hemorrhage, and where it is also associated with a very small mortality. Since we did not use blood pressure as a criterion for our selection of thrombosis, we regard this correlation as significant. It is pertinent from the investigations of Rasmussen and Boe[13] that the mortality due to cerebral vascular accident in cases of essential hypertension bears a distinct relation to the height of both systolic and diastolic blood pressures. They further emphasize the great prognostic significance of the height of blood pressure. The relationship drawn by them closely approximates our findings: in both studies not only is a rising mortality demonstrated with an increasing pressure, but the levels of systolic and diastolic pressures, at which the increased mortality is clearly manifest,

are similar. Although the purposes of the studies in these instances are quite different, a similar conclusion is reached, namely that the height of blood pressure significantly affects the prognosis of cerebral vascular accidents. The discrepancy in our series between the systolic and diastolic blood pressures as a factor affecting the outcome of these cases further suggests that the intermittent distending force of an elevated systolic pressure plays a greater role than the continuous stress due to the maintained diastolic level. With our thinking oriented by the cardiological concept of the major importance of the diastolic pressure, against which the heart labors, we have perhaps lost sight to some extent of the fact that the peripheral vasculature may be very severely taxed by the force of the systolic pressure wave. Courville indicates that, regardless of the nature of the predisposing focal lesion, gross cerebral hemorrhage is the result of rupture of an artery no longer able to withstand the intravascular pressure incident to cardiac systole. It is probable, therefore, that the difference in the relationship of systolic and diastolic pressures to mortality is due to their dissimilar effects upon the peripheral vasculature.

The ultimate prognosis of a case depends not so much upon the features peculiar to the case as upon our understanding of average expectations. Longevity, so far as the disease itself is concerned, will be determined by the recurrence of attacks and the mortality characteristic of the recurrences. Brown[2] carefully followed a series of 120 cerebral vascular hemorrhages with a mortality of 35% on the first attack which corresponds well with our 29.3%. This author indicates a rising mortality with subsequent attacks, whereas we found the same incidence in our first and second attacks of hemorrhage, 29.3% and 30% respectively, and could regard neither Brown's nor our own figures of third and fourth attacks as adequate for analysis. We cannot, therefore, fully agree that "the mortality in cerebral hemorrhage is directly proportional to the number of strokes the patient has had," especially since the rate of recurrence is low and the mortality does not vary. In our series, 18.8% proceeded to a second attack, so that the chances of death on a recurrence are approximately 1 in 5. If maximal overcompensation could be made for the unfollowed cases, the figure would rise to 34%, which is close to Brown's figure of 40% with second attacks. But more important is the fact that from both Brown's and our studies it may be concluded that the liability of death by a subsequent attack is less than half the rate encountered in the initial attack, or between 11% and 20%. Mortality in the second attack represents only 5.6% of the survivors.

With this estimation of the incidence of repeated attacks and mortality therefrom, the ultimate prognosis may be considerably narrowed. The expectation of life may be parallel to that of the person's age group, unless a recurrence and sequelae are such as to compromise vital functions, which is in part decided by the location and extent of lesions. Gintrac[6] in 1869 was perhaps the first to report on this phase of the problem when he stated that of 667 cases of hemorrhage, 106 lived to between 4 and 10 years, and 8 patients survived over 10 years. It was later observed by Charcot[3] that in an institution for the infirm, of 1,000 invalids, 200 were hemiplegics for some duration. In a commentary[11] upon the difference between the numbers of cases of cerebral vascular accident clinically controlled and those analysed by autopsy, of which there were 604 and 245 respectively, it is pointed out that these two contrasting groups empha-

size the fact that cerebral vascular accident does not always carry with it a fatal outcome. It is further indicated that many patients may survive 10 years and even longer. In our small series, 3 have survived for over 10 years, one of these for 25 years, 6 other patients are alive after 5 years and the remainder for variable shorter times. Brown mentions a case surviving for 18 years. A considerable survival is possible, though very long intervals are uncommon. However, since the extent of the damage, its location and the age of incidence are most probably very important factors in longevity, an exact appraisal can come only from an extensive accumulation of such data. Since the majority of these accidents occur in the geriatric period of life, their longevity may be most accurately assessed by close comparsion with their contemporary collaterals. By this it is feasible to determine how short they fall of their life expectancy and whether the demise is directly attributable to the cerebral vascular accident. Our indications suggest that these patients have a good chance of living out their expected life span once they survive the initial attack and suffer no recurrences.

Summary and Conclusions. 1. The correlation of clinical data concerning age, sex, blood pressure and physical signs has been made on 75 cases of cerebral hemorrhage, 27 of thrombosis and 5 of embolism. Of these, 64.5% were followed up successfully.

2. In the assessment of immediate prognosis, age, the duration of coma, type of respiration, and an elevation of blood pressure offered valuable assistance. The type of accident is also important, since 30% of hemorrhages and 7.5% of thromboses are fatal in the first attack.

3. Of the survivors of hemorrhage about 18% have one or more recurrences; 5.6% of these die in the second attack and 11% of the combined subsequent attacks. Unless seriously compromised by the sequelae of the disease, the remaining survivors seem to live out their expected life span.

REFERENCES

1. **Aring, C. D.**, and **Merritt, H. H.**: Arch. Int. Med., **56**, 435, 1935.
2. **Brown, C. H.**: Medical Record, **154**, 22, 1941.
3. **Charcot, J. M.**: Clinical Lectures on Seni'e and Chronic Diseases. Transl. by W. S. Tuke. Vol. 95, p. 262, Pub. of New Sydenham Society, London, 1881.
4. **Courville, C. B.**: Pathology of the Central Nervous System, Pacific Press Publ. Assn., Mountain View, Cal., 1937.
5. **Drozda, J. V.**: Wien. med. Presse, **21**, 300, 1880.
6. **Gintrac, E.**: Traité théoretique et pratique de l'appareil nerveux, vol. 2, p. 467, Paris, Germer-Baillière, 1869.
7. **Jones, A. E.**: Brain, **28**, 527, 1905.
8. **Levy, L. K.**: New Orleans Med. and Surg. J., **92**, 683, 1939-1940.
9. **MacDonald, R. H.**: Med. Clin. N. Am., **22**, 479, 1938.
10. **Merritt, H. H.**: Med. Clin. N. Am., **22**, 577, 1938.
11. **Merritt, H. H.**: New York State J. Med., **48**, 2371, 1948.
12. **Newbill, H. P.**: J. Am. Med. Assn., **114**, 236, 1940.
13. **Rasmussen, H.**, and **Bøe, J.**: Acta Med. Scand., **120**, 12, 1945.
14. **Spiller, W. G.**: J. Am. Med. Assn., **51**, 2101, 1908.
15. **Weiss, S.**: Med. Clin. N. Am. **13**, 111, 1929.

MAJOR ETIOLOGICAL FACTORS PRODUCING DELAYED RESOLUTION IN PNEUMONIA*

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The patient with pneumococcal pneumonia, treated with penicillin or the sulfonamides, generally responds with dramatic clinical improvement within a few days, and shows complete resolution manifested by disappearance of physical and roentgenological signs within a period of 2 to 4 weeks. Cases frequently occur, however, in which this uneventful and desirable course does not ensue. In an attempt to determine the factors responsible for delayed resolution, a study has been made of 198 cases of pneumonia admitted to this hospital during its first 2 years of operation. The hospital has been designated as a chest center for the Veterans Administration, and 47 of the above patients who were received had been treated for pneumonia prior to admission. Of these 198 cases, 52 (26.2%) exhibited delayed resolution.

Delayed resolution or unresolved pneumonia includes a number of different pathological conditions. It is a useful clinical term and not an expression of a specific pathological entity. It must be emphasized that the term should not be employed without being qualified by a pathological or bacteriological explanation. In selecting cases for this series, an arbitrary time limit for complete resolution was set at 30 days.

It is rather surprising to note the paucity of published reports on this subject. A review of the British and American literature during the last 20 years reveals only three articles pertaining specifically to the etiology of unresolved pneumonia[1,4,5]. This is almost certainly due to the fact that many of the so-called unresolved pneumonias, on reaching the pathologist, are correctly classified as to their proper etiology: for example, malignancy, lung abscess, bronchiectasis, lipoid pneumonia, and others. Although many of the cases of delayed resolution have their origin in underlying disease, instances occur in which no obvious basis can be detected for the delay in proceeding to complete resolution. These must fall in the group of chronic pneumonias. The etiological factors responsible for this delay may not be readily apparent, but on more thorough and detailed study can be demonstrated in almost every instance. Pickhardt[4], in 1928, studied 46 patients with chest

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conditions in whom a diagnosis of unresolved pneumonia had been made, and he was able to determine the specific disease process present in all but 6 cases. Of this series, 37.5% proved to be surgical conditions.

The consideration of etiology must involve a discussion of 3 groups of factors. The first of these is the group of bacteriological and chemical factors (Table 1). *Klebsiella pneumoniae*,

TABLE 1. BACTERIOLOGICAL AND CHEMICAL FACTORS IN DELAYED RESOLUTION

1. Klebsiella pneumoniae (Friedlander's Bacillus)
2. Diplococcus pneumoniae—Type III
3. Streptococcus
4. Staphylococcus
5. Pasteurella tularensis
6. Mycobacterium tuberculosis
7. Anerobic organisms of the oropharynx
8. Viruses: a. Primary atypical pneumonia
   b. Ornithosis
9. Fungi
10. Aspiration of food or gastric contents
11. Oil aspiration
12. Septic embolism

Diplococcus pneumoniae—type III, Streptococcus, and Staphylococcus are organisms known for their tendency to produce severe and protracted pneumonias in which suppuration and abscess formation often occur. The Streptococcus and Staphylococcus also possess a strong tendency to produce pleural effusion and empyema. If tularemic infections are not recognized and promptly treated with streptomycin, their course is prolonged. It is rather a common occurrence for a tuberculous pneumonia to go unrecognized in its early stages. The spirochetes and other anerobic organisms of the oropharynx frequently are aspirated during anesthesia, diabetic coma, alcoholic stupors and other forms of unconsciousness. This is particularly likely to occur in individuals with pyorrhea alveolaris. The resulting pneumonias are slow to resolve because of the necrotizing nature of the infection. Aspiration of food and secretions from the dilated esophagus of the patient with cardiospasm occurs not uncommonly and produces a relatively benign organizing pneumonia, as contrasted with the extensive suppuration and destruction seen with aspiration of acid gastric contents. Many patients with primary atypical pneumonia show pulmonary infiltration over prolonged periods of time. Chronic fungus infections of the lungs are being recognized with increasing frequency. Aspiration of oil produces a chronic organizing process. Septic embolism should be suspected in protracted migratory pneumonias of lobular distribution in which a single organism is repeatedly isolated from the sputum[1]. There is usually an obvious source of infection elsewhere in the body. The importance of obtaining an early and accurate bacteriological study is much greater now than in the era before antibiotics, since it is mandatory to employ the available specific drugs against the invading organism.

The second major group of processes responsible for delayed resolution includes all the factors which impair bronchial drainage. This includes any condition which obstructs the upper or lower respiratory tract, interferes with normal ciliary action within the bronchus, or impairs the normal mobility and elasticity of the lung parenchyma.

A classification of the factors producing impaired bronchial drainage is given in Table 2. The important endobronchial causes are carcinoma in the older age group and foreign bodies in infants and children. It cannot be emphasized too strongly that, in a patient over the age of 40 with a protracted pneumonia or a history of recurrent attacks of pneumonia involving the same lobe, carcinoma must be seriously considered. This is especially true if a history of blood-streaked sputum or unilateral wheeze is obtained. If bron-

TABLE 2. FACTORS INFLUENCING BRONCHIAL DRAINAGE LEADING TO DELAYED RESOLUTION

1. Upper respiratory obstruction:
   A. Vocal cord paralysis
   B. Pharyngeal paralysis
2. Bronchial obstruction:
   A. Endobronchial disease
      1. Tumor: a. Carcinoma
                b. Adenoma
      2. Foreign Body
      3. Inflammatory disease:
         a. Tuberculosis
         b. Non-specific stenosis
   B. Extrabronchial disease
      1. Aneurysm
      2. Mediastinal tumor
      3. Hilar node enlargement
3. Impaired ciliary action:
   A. Chronic bronchitis
   B. Bronchiectasis
   C. Bronchial asthma
   D. Arrested pulmonary tuberculosis
4. Impaired pulmonary mobility:
   A. Pulmonary fibrosis and emphysema
   B. Pneumoconiosis
   C. Chest trauma
   D. Paralysis of diaphragm or intercostal muscles.

choscopy does not reveal the neoplasm, examination of the bronchial washings and sputum for tumor cells by the Papanicolaou technique may yield the diagnosis. However, the failure to obtain positive evidence of the presence of carcinoma by these methods should in no way delay exploratory thoracotomy. This approach has recently been emphasized by Ochsner and his associates[3]. Extrabronchial masses may occasionally compress the lumen of a bronchus, thereby producing inadequate drainage and secondary pneumonia.

Impaired ciliary action resulting in poor drainage of the lung, puddling of secretions, and pulmonary infections which are slow in clearing are seen in patients with bronchitis, bronchiectasis and asthma. This process may also occur in lobes which were once the site of a tuberculous process. Fibrosis, emphysema and inadequate blood supply with impaired aeration of the region undoubtedly play an important role.

There is little doubt that the ventilation and drainage of the peripheral lung tissue are greatly impaired in conditions in which pulmonary mobility is lessened. The fibrotic and emphysematous lung has little elasticity, and the force of the expiratory air blast, which helps expel secretions from the alveoli and bronchioles, is impaired. The peristaltic action of the bronchioles is also diminished, adding further to the inadequate cleansing of the affected broncho-pulmonary segment. The same mechanism is present in patients whose pneumonia is associated with chest trauma. Here the lung is splinted by fractured ribs and pleurisy, and bronchospasm and interstitial hemorrhage are prominent features. If adequate amounts of an analgesic drug are administered, or, better yet, if regional nerve blocks are performed to relieve the pain, the effects of trauma may be minimized. Finally, it is apparent that poliomyelitis and other neurological diseases which produce paralysis of the diaphragm, the intercostal, the laryngeal, or the pharyngeal musculature may cause delayed resolution by interference with bronchial drainage.

The intrinsic complications of the pneumonic process (Table 3) were the

TABLE 3. INTRINSIC COMPLICATIONS OF THE PNEUMONIC PROCESS

1. Pleural effusion
2. Empyema
3. Lobar or segmental collapse (atelectasis)
4. Lung abscess

most common causes of protracted resolution in the younger age group. These are closely associated with the factors already discussed. Scadding[5] pointed out that chronic suppurative pneumonia rarely follows pneumococcal pneumonia, but was unable to cor-

relate the bacteriology with the clinical course in his cases. Although pleural effusion is not uncommon in the more severe pneumonias, no case initially treated by us developed empyema.

The major etiological process responsible for delayed resolution was determined in 50 (96.1%) of the 52 cases (Table 4). Many of the older patients

TABLE 4. DISTRIBUTION OF 52 CASES OF DELAYED RESOLUTION ACCORDING TO MAJOR ETIOLOGICAL PROCESSES

Impaired Bronchial Drainage	22
Bacteriological and Chemical Factors	16
Intrinsic Complications of the Pneumonic Process	12
Undiagnosed	2
Total	52

presented multiple etiological factors. Each has been classified under the one factor considered largely responsible for the delay in clearing. It is to be noted that in not quite half of our patients impaired bronchial drainage was the significant process causing delay.

A specific organism or chemical insult was responsible for the delay in 16 (30.7%) patients (Table 5). Aspiration was the most common cause, and 5 of the 6 patients developed single or multiple lung abscesses, 4 of which were removed surgically. Friedlander's pneumonia occurred in 4 patients, all of whom recovered under streptomycin therapy. Of the 2 cases in which delay in clearing was considered secondary to oil aspiration, one followed the instillation of the iodized oil for diagnostic purposes. The second case was a typical example of lipoid pneumonia in a patient who lubricated his permanent tracheotomy opening with mineral oil several times daily over a period of many years.

TABLE 5. DISTRIBUTION OF 16 CASES OF DELAYED RESOLUTION OF PRIMARY BACTERIOLOGICAL AND CHEMICAL ETIOLOGY

Aspiration of Anerobic Organisms of the Oropharynx	6
Klebsiella pneumoniae	4
Oil Aspiration	2
Mycobacterium tuberculosis	2
Streptococcus	1
Primary Atypical Pneumonia	1

Impaired bronchial drainage was responsible for the delay in 22 (42.3%) cases (Table 6). Four of these cases were proven to be due to bronchogenic carcinoma. All 4 of these patients whose early diagnosis and definitive treatment were delayed for some months by treatment for pneumonia proved to be non-resectable and have since died. The other frequent cause of delayed resolution in this group was pulmonary fibrosis and emphysema. The 5 patients with this condition required months for resolution to occur, but finally cleared completely. One of this group has since suffered a second pneumonic episode in the same lung, which again was slow in resolving.

TABLE 6. DISTRIBUTION OF 22 CASES OF DELAYED RESOLUTION DUE TO IMPAIRED BRONCHIAL DRAINAGE

Emphysema and Fibrosis	5
Bronchogenic Carcinoma	4
Arrested Pulmonary Tuberculosis	3
Chest Trauma	2
Chronic Bronchitis	2
Bronchial Asthma	2
Non-specific Bronchial Stenosis	1
Pneumoconiosis	1
Hilar Node Enlargement	1
Paralysis of Laryngeal and Pharyngeal Muscles	1

The last group of cases to be con-

TABLE 7. DISTRIBUTION OF 12 CASES OF DELAYED RESOLUTION DUE TO INTRINSIC COMPLICATIONS OF THE PNEUMONIC PROCESS

Lung Abscess	4
Lobar or Segmental Collapse (Atelectasis)	4
Pleural Effusion	2
Empyema	2

sidered is that in which delay was caused by intrinsic complications of the pneumonic process itself (Table 7). Twelve patients (23%) fall in this category. These generally consisted of younger patients with extensive lesions, whose treatment was instituted late or who received inadequate initial treatment without adequate bacteriological study. It is possible that the cases listed here as lung abscess might have been more properly classified under other headings if they had been studied in an earlier phase of their disease. The group listed as lobar or segmental collapse is easily the most difficult to evaluate. An element of atelectasis is probably present in all pneumonias. Coryllos and Birnbaum[2] have set forth the concept that lobar pneumonia is a pneumococcic atelectasis due to bronchial obstruction by mucus infected with virulent pneumococci. We have no adequate explanation for the prolonged presence of collapse in these 4 patients, despite active therapy with bronchodilator drugs and bronchoscopic aspiration.

The 2 patients in whom no clear, underlying factor could be demonstrated included a young man with extensive miliary nodular disease of the lungs of undetermined origin. The second case was that of an elderly man with pernicious anemia who suffered an extremely severe lobular pneumonia involving the entire right lung.

It will be noted from this review that in almost every instance of delayed resolution one or more local etiological factors could be found to account for the phenomenon. The most significant finding of this entire study appears to be the fact that of 52 cases of delayed resolution, 4 cases (7.7%) were proven to be due to bronchogenic carcinoma*. It seems clear, therefore, that bronchogenic carcinoma should occupy a prominent place in the differential diagnosis of delayed resolution in pneumonia. No sounder advice can be offered to the clinician than Amberson's statement[1], "It should be the inflexible rule of the clinician never to make a diagnosis of unresolved or organizing pneumonia without searching for the cause; otherwise, patients with serious and remediable lesions of the lungs may miss the opportunity of early diagnosis and cure."

Summary. 1. The major etiological factors producing delayed resolution in pneumonia have been determined in 50 (93.1%) of 52 cases studied.

2. The major process responsible for delayed resolution was found to be impaired bronchial drainage in 22 cases (42.3%); in 4 cases, this was directly the result of bronchogenic carcinoma. A specific organism or chemical insult was responsible in 16 cases (30.7%). Intrinsic complications of the pneumonic process caused delayed resolution in 12 cases (23%).

REFERENCES

1. **Amberson, J. B.**: J. Mich. State Med. Soc., **42**, 599, 1943.
2. **Coryllos, P. N., and Birnbaum, G. L.**: Am. J. of Roentgenol., **22**, 401, 1929.
3. **Ochsner, O., DeBakey, M., and Dixon, J. L.**: J. Am. Med. Assn., **135**, 321, 1947.
4. **Pickhardt, O. C.**: Arch. Surg., **16**, 192, 1928.
5. **Scadding, J. G.**: Proc. Roy. Soc. Med., **31**, 1259, 1938.

* Since the compilation of this report 3 more patients have been studied who were treated for pneumonia for varying periods, and who have been proven to have bronchogenic carcinoma as the etiological factor.

THE TREATMENT OF FALCIPARUM MALARIA WITH INTRAMUSCULAR CHLOROQUINE

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Culwell *et al.*[6] have recently demonstrated the efficacy of intramuscular chloroquine in 16 cases of sporozoite induced, Chesson strain, *vivax* malaria. The antimalarial action of the drug was comparable to that resulting from oral administration and no toxic reactions were observed. When given orally chloroquine has been found to be highly effective in the treatment of all types of malaria[4-6,8,10-12] and the toxicity less than that following quinine or quinacrine administration[1,2,4,7,10].

There is no report of *naturally* acquired falciparum malaria treated with parenteral chloroquine. We have treated 8 patients with falciparum malaria with chloroquine intramuscularly. All of these patients acquired their infection in Africa and 6 had received suppressive or therapeutic quinacrine or quinine prior to admission to the hospital. The longest period that elapsed between the last administration of antimalarial drugs and treatment with parenteral chloroquine was 42 days; the shortest was 12 days. After the diagnosis was confirmed by blood smear each patient was given an intramuscular injection of 0.2 gm. of chloroquine base in 5 cc. of sterile unbuffered aqueous solution according to the method of Culwell *et al.*[6]. One patient (Case 8) received an additional dose of 0.2 gm. intramuscularly 3 days after initial administration of the drug. Daily parasite counts were done on each patient and 2 to 5 days later each patient was given a routine course of oral chloroquine as recommended by Most *et al.*[10]. Results of treatment are summarized in Table 1.

No adverse local or systemic effects from the intramuscular chloroquine were observed in any of these patients; toxic effects following the parenteral administration of quinine or quinacrine are not infrequent. Rapid clearing of the parasites from the peripheral blood occurred although none of the patients had very high initial parasite densities. The most striking feature of treatment with parenteral chloroquine in this series was that in 6 of the 8 patients no asexual falciparum parasites were found in the blood after administration of the initial dose. The remaining 2 patients showed only 30 and 60 ring forms on the morning of the day further therapy was given. It is likely that the blood of these patients would likewise have cleared completely if further therapy had been delayed. Four of the 8 patients showed

gametocytes in their smears after their blood was free of asexual parasites. Neither the intramuscular nor oral chloroquine had any apparent effect on the sexual forms.

The clinical response of these patients to intramuscular chloroquine was likewise very striking. All of them became completely afebrile in 1 to 2 days and were markedly improved subjectively. Nausea and vomiting which had occurred in 3 patients subsided promptly following the initial therapy.

The effect of previous antimalarial medication in these patients cannot be definitely determined. It is not likely, however, that this medication had any effect on their response to intramuscular chloroquine since there was a period of from 12 to 42 days from the time the patients last took quinine or quinacrine until chloroquine was given.

It has been recommended that malaria with persistent vomiting, coma, impending coma or a high density of falciparum parasites in the blood smears (5% or more of red cells infected) be treated with parenteral antimalarial drugs[3]. Although none of the patients in this series showed a high parasite density, 3 of them had nausea and vomiting severe enough to prevent administration of oral medication. None of the patients had symptoms of cerebral malaria nor were any in coma. Culwell *et al.*[6] pointed out that none of the patients treated by them were critically ill and that it was impossible to conclude from their series that chloroquine given intramuscularly would prove rapidly efficacious in overwhelming infections where there is peripheral vascular stasis. Since none of our patients were critically ill, either, no definite conclusions can be reached as to the route of administration of the drug in this type of patient. Culwell *et al.*[6] suggested that chloroquine could be given in a saline infusion intravenously over the course of 3 to 4 hours for the treatment of patients critically ill with falciparum malaria as carried out by Machella *et al.*[9] with quinacrine and SN 6911. The parenteral administration of chloroquine is not recommended for patients who can take the drug by mouth except for those who show very high parasite densities[3], as the absorption of chloroquine from the alimentary tract is usually very rapid.

TABLE 1.—CLINICAL AND PARASITOLOGICAL RESPONSE IN 8 ATTACKS OF NATURALLY ACQUIRED FALCIPARUM MALARIA TREATED WITH INTRAMUSCULAR CHLOROQUINE

Case Number	Attack Number	Parasite count per cu. mm. on day of therapy	Parasite count on second day	Parasite count on third day	Parasite count on fourth day	Parasite count on fifth day	Parasite count on sixth day	Days to negative smear (for asexual forms)	Days until afebrile <37.0°C (<98.6°F.)
1	2	positive (no count made)	9,720	3,000	—	0	—	4	1
2	3	6,380	1,330	0	0	—	—	2	1
3	1	7,080	300	60	0	—	—	3	2
4	1	20,750	—	2,457	—	30	0	5	1
5	2	9,590	5,400	420	0	0	0	3	2
6	1	6,120	2,530	0	0	0	0	2	1
7	3	1,560	490	60	—	0	0	4	2
8	3	19,500	14,630	4,190	0	0	0	3	1

The following case history illustrates the type of response obtained with intramuscular chloroquine in this series:

Case Abstract—CASE 5. S. C., a 32 year old seaman was admitted to the hospital on

September 18, 1948, complaining of chills and fever. About 2½ months before admission he had sailed for Africa. Three days before arriving in Africa, about 2 months before admission, he began to take a capsule of quinine daily. He did not know the amount of quinine in the capsule. His ship touched various ports along the west coast of Africa during a period of about 1½ months. The patient was ashore in many of these ports in the evening and overnight. He continued to take quinine but, about 15 days before admission, he had onset of chills, fever, nausea, and vomiting. At this time he was seen by a physician in the Canary Islands. His quinine was discontinued, and he was given some "white pills" by the physician. He was incapacitated for 5 days, but after this resumed his duties and felt well until the day before admission when he again had chills, fever, nausea, and vomiting.

Physical examination on admission showed a well developed and nourished white male in no acute distress. His temperature was 38.7° C. (101.5° F.), pulse 100, and blood pressure 115/80. Except for a deformity about the orbit, the result of an old injury, physical examination was essentially negative.

Laboratory examinations showed that the hemoglobin was 12.0 gm., red cell count 3,800,000, white cell count 7,500 (68% neutrophils, 22% lymphocytes, 8% monocytes, and 2% eosinophils). The Kahn precipitation test and Cardio-Lipin test were negative. Smears were positive for plasmodium falciparum.

After admission the patient's fever continued, although on one occasion it dropped to normal (Fig. 1). About 36 hours after admission, the patient had a chill, nausea, and vomiting, and his temperature rose to 39.5° C. (103.4° F.). At this time he was given 0.2 gm. of chloroquine intramuscularly. Within 40 hours the patient had become afebrile and felt well. He had no complaints and remained essentially afebrile during the rest of his hospitalization. His smears became negative for malarial parasites in 2 days, and remained negative. Seven days after admission (5 days after parenteral administration of chloroquine) oral chloroquine was begun. He received 1.5 gm. of chloroquine base in 4 days. He was discharged from the hospital on September 28, 1948.

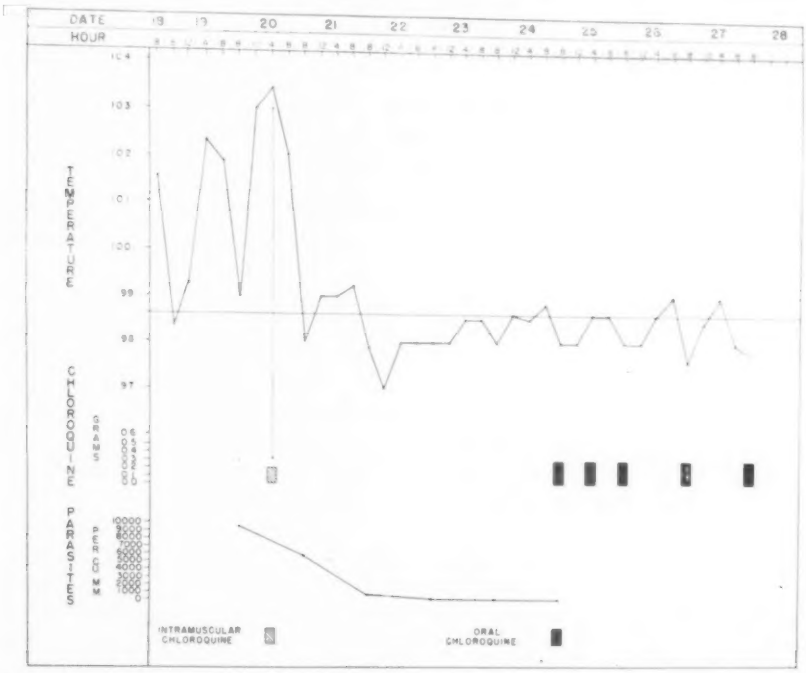

Fig. 1. S. C. (Case 5). Effect of chloroquine on the temperature and parasitemia in a case of falciparum malaria.

Summary. 1. Eight patients with naturally acquired falciparum malaria were treated with intramuscular chloroquine.

2. All of the patients responded well to treatment and there was rapid clearing of the asexual parasites from the blood.

3. No local or systemic toxic effects from the drug were observed.

REFERENCES

1. **Alving, A. S., Eichelberger, L., Craige, B., Jr., Jones, R., Jr., Whorton, C. M.,** and **Pullman, T. N.:** J. Clin. Invest., **27**, 60, 1948.

2. **Berliner, R. W., Earle, D. P., Jr., Taggart, J. V., Zubrod, C. G., Welch, W. J., Conan, N. J., Bauman, E., Scudder, S. T.,** and **Shannon, J. A.:** J. Clin. Invest., **27**, 98, 1948.

3. Bull. U. S. Army Med. Dept.: **4**, 286, 1945.

4. **Ibid.**, **7**, 835, 1947.

5. **Coatney, G. R., Ruhe, D. S., Cooper, W. C., Josephson, E. S.,** and **Young, M. D.:** Am. J. Hyg., **49**, 49, 1949.

6. **Culwell, W. B., Cooper, W. C., White, W. C., Lints, H. A.,** and **Coatney, G. R.:** J. Nat. Malaria Soc., **7**, 311, 1949.

7. **Gordon, H. H., Dieuaide, F. R., Marble, A., Christianson, H. B.,** and **Dahl, L. D.:** Arch. Int. Med., **79**, 365, 1947.

8. **Loeb, R. F., *et al.*:** J. Am. Med. Assn., **130**, 1069, 1946.

9. **Machella, T. E., Kimmelman, L. J.,** and **Lewis, R. A.:** Bull. U. S. Army Med. Dept., 4, 286, 1945.

10. **Most, H., London, I. M., Kane, C. A., Lavietes, P. H., Schroeder, E. F.,** and **Hayman, J. M., Jr.:** J. Am. Med. Assn., **131**, 963, 1946.

11. **Pullman, T. N., Craige, B., Jr., Alving, A. S., Whorton, C. M., Jones, R., Jr.,** and **Eichelberger, L.:** J. Clin. Invest., **27**, 46, 1948.

12. **Young, M. D.,** and **Eyles, D. E.:** Am. J. Trop. Med., **28**, 23, 1948.

LOCALIZED SEALED-OFF PERFORATION IN RECURRENT DUODENAL ULCER

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Acute perforation of a peptic ulcer usually produces a typical clinical picture that offers little diagnostic difficulty. There is usually "an acute surgical abdomen" with free gas in the peritoneal cavity. The free gas is demonstrated beneath both domes of the diaphragms in the majority of cases. Another variety of perforation is the "Formes Frustes" reported by Singer and Vaughan[1]. In the latter condition an acute surgical condition is present in the abdomen, often with free air in the peritoneal cavity. This subsides after a number of hours, leaving the patient in comparative comfort. In both varieties of perforation there is acute abdominal pain, prostration, shock, and a board-like rigid abdomen. In the type of sealed-off perforation reported here, severe symptoms and shock were absent, the patients were ambulatory. There is no free air in the peritoneal cavity.

There are 3 types of walled-off perforations: 1, a medical type; 2, a surgical type; and 3, chronic perforation with an accessory pocket. Only the first variety will be discussed in this communication. Five such cases are here reported.

The sealed-off medical variety of perforation must occur with greater frequency than is suspected. This complication, although mild, has not often been recognized. There is a dearth of information on this type of perforation complicating the ambulatory case of duodenal ulceration. The actual incidence has never been computed, probably because sealed-off perforations of this type are best demonstrated by special methods of examination. Within a 3 months' period, approximately 65 cases of duodenal ulcer in all stages were examined. Among these there were 5 of this form of perforation. These patients presented clinical symptoms which were more pronounced and lasted longer than any the patient had previously experienced. Although this is too brief a period and too small a series to establish its incidence, it is nevertheless possible to demonstrate its existence and emphasize the frequency of this condition. Since these cases represented a selected group, the true incidence cannot as yet be established. If one would examine all intractable duodenal ulcer cases, in the erect position, utilizing the spot film compression technique, many cases of sealed-off localized perforations would be detected. The 5 cases of recurrent duodenal ulcer presented in this communication had been selected for spot film examination because of their clinical history of an abrupt onset of an unusual mild digestive episode.

The subhepatic gas-bubble is not a new sign for walled-off perforations. Attention is now being directed to a pinpoint sealed perforation of a medical type, its incidence and the roentgenologic method to demonstrate them.

The following 5 cases are presented to show the characteristic clinical and roentgen picture of a medical type of walled-off minimal pinpoint perfo-

ration which had spontaneously sealed itself.

Case Reports. CASE 1. A man, aged 52, first had an ulcer 25 years ago. At intervals since then there were complaints of epigastric pain, relieved by food, which awakened him during the night. He felt well, with few symptoms, until about 1 year ago, when he began to have symptoms refractory to the usual treatment. Recently he had an acute episode that differed from any experienced before. The usual ambulatory treatment did not give complete relief. Roentgen-ray examination revealed a markedly deformed duodenal bulb with an ulcer-niche filling defect. Situated above the duodenal bulb and outside the duodenal contour was a persistent localized small air-pocket. This was to be adherent by extensive adhesions beneath the liver. There was evidence of chronic inflammatory changes involving the serosa and a matting together of adjacent tissues surrounding the suspected old pinpoint perforation. The duodenal bulb revealed evidence of a chronic ulceration. Arising from the inner aspect of the bulb, there was a pseudodiverticulum or an accessory pocket of a perforation which was not observed in the previous roentgen examination.

CASE 2. Man, aged 48, had recurrent symptoms of a duodenal ulcer for 15 years. Frequent follow-up examinations showed complete healing and cicatrization of the ulcer, with varying degrees of gastric retention. Until recently, he had few symptoms and no changes in the anatomic appearance of the healed ulceration. In a recent episode

FIG. 1. CASE 1. (A) Roentgenogram made in the erect position with spot film compression. A markedly deformed duodenal bulb with a large air-bubble above the duodenum is shown at arrows. Note the flattened base of the air-pocket, due to a small amount of fluid. (B) Same case, with roentgenogram made in the recumbent prone position without compression. No gas pocket can be demonstrated.

demonstrated only in the erect position. A diagnosis of a minute blowout type of walled-off perforation was made. He was hospitalized at the Church Home Hospital for a few weeks and obtained complete relief of symptoms. Re-examination made 3 and again 11 months later did not show any sign of perforation. The encapsulated air-pocket had disappeared.

This patient remained clinically well for almost 1 year, when his ulcer symptoms recurred. Because of the repeated episodes of the intractable ulcer, he was re-admitted to the Church Home Hospital for surgical exploration. At operation the duodenum was found there was a recurrence of symptoms that lasted longer than any he had experienced before. Roentgen-ray examination at this time showed a recurrence of activity with an ulcer niche defect. There was about a 10% gastric residue in 5 hours. A small air-bubble was demonstrated directly above the duodenal bulb which was due to a recent pinpoint sealed-off perforation. This encapsulated air was only seen in the erect position. No barium was seen to enter the pocket. A diagnosis of a sealed-off perforation of a duodenal ulcer was made, which accounted for the recurrence of atypical symptoms.

This patient returned for re-examination 6

months later. At this time he had no digestive symptoms and felt comparatively well. A check-up examination showed that the ulcer niche and the gas-bubble had disappeared.

Case 3. A 53 year old man had stomach trouble for 10 years, with periodic pains relieved by food, characteristic of duodenal ulcer. Recently his symptoms suddenly became worse, and were different from any he had had before. They were more severe and lasted longer than in any other previous attack. The spell was not severe enough to keep him from working, although the vomiting had weakened him considerably. He had never vomited before this episode. Roentgen-ray examination revealed evidence of a duodenal deformity with an ulcer-niche defect. A small encapsulated air-pocket was demonstrated above the duodenal bulb, only in the erect position. The diagnosis of a minute blowout type of walled-off sealed perforation was made.

Case 4. A man, aged 40, had coronary heart disease for 6 years. His onset of digestive trouble began 5 years ago with attacks of abdominal pain, without food relation. The pain was severe, radiating between the shoulder blades, requiring morphine for relief. Between the attacks he felt well. His appetite was good. There was no loss of weight. Roentgen studies of the gastrointestinal tract at this time revealed a duodenal ulceration. Three years later a gallbladder study revealed a large number of small gallstones. He was operated upon 1 year ago and the gallstones were removed; this was followed by complete relief from his acute abdominal attacks. About 6 months later his ulcer symptoms suddenly recurred, with abdominal pain, which awakened him during the night. A gastrointestinal study made at this time revealed a pyloro-duodenal deformity due to an ulceration, associated with a redundant prolapsing gastric mucosa. A small gas-bubble was observed above the superior aspect of the duodenum. This suggested a recent escape of a small amount of air from a pinpoint perforation which had spontaneously sealed itself, and became walled off in the subhepatic area.

Case 5. A man, aged 49, had digestive trouble for 15 years. The predominant symptoms were pyrosis and pains across the upper abdomen. His appetite was good and he always felt better when he ate. He had an appendectomy without relief and later a gallbladder operation. The last digestive episode began 1 week before admission with epi-

Fig. 3

Fig. 3

Fig. 2. Case 2. Demonstrates a deformed contracted cap with an ulcer niche defect at arrow. Note the air-bubble with a flattened base, atop the bulb at arrows.

Fig. 3. Case 3. An elongated deformed duodenal bulb is shown. Note the small subhepatic air-bubble above the duodenal bulb at arrows.

gastric distress and pain. There was no food relief. Ordinary treatment did not help him as it had before. Because this spell of indigestion lasted longer than usual, he sought medical attention. A gastrointestinal Roentgen-ray examination revealed a deformed duodenal bulb due to an ulceration. No ulcer niche defect could be demonstrated. Atop the duodenal bulb, the erect compression spot film showed a persistent small air-bubble about the size of a chestnut. A diagnosis of recurrent duodenal ulceration with a sealed-off perforation was made.

Discussion. Clinically, this form of perforation more commonly occurs in cases of recurrent duodenal ulceration. The attacks are usually mild and transient. In most instances the symptoms are more exaggerated but the possibility of a perforation is not ordinarily considered. These patients do not obtain relief with food, soda or antispasmodics as quickly as they had previously. The patient is of the opinion that a new condition has occurred for which he seeks medical attention. There is usually persistent pain in the epigastrium, somewhat to the right of the mid-line. The pain lasts longer than usual, tends to become milder and intermittent. Later there is a persistent soreness and discomfort in the epigastrium. At times food increased the discomfort. Vomiting frequently occurred during the episode.

Five ambulatory cases of a pinpoint, spontaneously sealed-off type of perforation occurring in recurrent duodenal ulceration were observed. The symptoms presented were not severe, but differed from those the patients had previously experienced. All of the 5 cases were males. There was an ulcer deformity of the cap in all of the cases and in 3 an ulcer niche defect was demonstrated. In all 5 cases there was a small, well defined encapsulated air-bubble situated above and outside of the duodenal bulb. All of these cases presented a persisting digestive episode.

FIG. 4

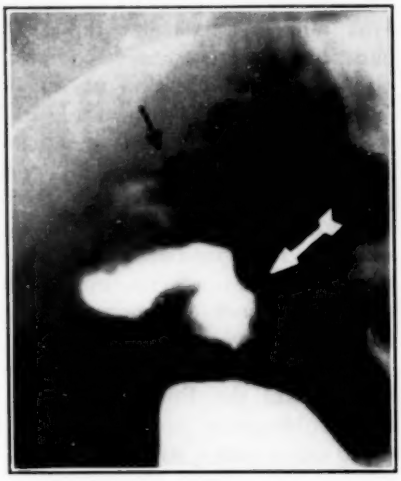

FIG. 5

FIG. 4. CASE 4. Illustrates a small gas-bubble atop the duodenal bulb. The amount of air in the gas pocket is minimal, could only be demonstrated on the erect spot compression films.

FIG. 5. CASE 5. A markedly deformed duodenal bulb with a small subhepatic air-bubble shown at arrows.

The duration of their ulcer symptoms ranged from 5 to 25 years.

This type of perforation in which there is an abrupt or insidious pinpoint blowout with spontaneous sealing-off of the perforation and walling off of the adjacent tissues, is thought to account for the subhepatic air-bubble. Occasionally, a small amount of fluid capped with air is seen in the base of the pocket. These perforations must be of pinpoint size permitting only air to escape. In none of the cases of this form of perforation had the barium meal escaped into the pocket. It is interesting to point out that the gas-bubble with a minimal amount of air was only demonstrated in the erect position under compression, while in the recumbent position no air pocket was observed. The gas-bubble in these cases could not be clearly demonstrated under the fluoroscope in any position. No communication was seen between the ulcer and the encapsulated air-pocket. The gas-bubble is generally small, smooth in contour with its superior aspect dome-shaped and its base flat above the duodenal contour. The similarity of the clinical manifestations and the Roentgen-ray picture of a subhepatic gas-bubble in all of the 5 cases was a striking feature. The gas-bubble usually disappears within a few weeks of treatment.

Multiple perforations may occur in some patients. How many sealed-off perforations occur during the life cycle of a case of duodenal ulceration is not known. However, it is most likely that multiple perforations of this type do occur in some instances. In Case 1, there were 2 perforations: a pinpoint sealed type, and later an accessory pocket type.

The purpose of this communication is to give information regarding a medical type of perforation that has not been demonstrated before. The following fundamental data are presented: 1, pinpoint leak-type perforations not uncommonly complicate chronic recurring duodenal ulceration; 2, it is associated with an active duodenal ulceration; 3, the subhepatic gas-pocket is an abnormal finding; 4, the gas-pocket is a roentgenologic observation.

The type of perforation considered in this paper was of a mild and transient nature presenting a medical problem. In 1 of the 5 cases there was surgical confirmation of the condition. Gas pockets outside of the duodenum are normally not observed unless there is a perforation, an air filled diverticulum or overshadowing gaseous viscus. The gas pocket in these cases cannot be considered as trapped air within the duodenum as it is distinctly outside of the duodenal contour. Because of the minimal amount of air which escapes from the pinpoint duodenal perforation, the condition is best demonstrated in the upright position. In the type of perforation discussed no barium entered the sac. The amount of air visible within the gas pocket depends upon the stage and time interval following the perforation. This small amount of air and, occasionally, fluid is usually absorbed, leaving no Roentgen evidence of the condition in later examinations.

In the differential diagnosis, other subhepatic gaseous shadows must be eliminated. The following conditions should be differentiated: 1, gas in a loop of colon (hepatic flexure); 2, gas in a loop of duodenum, such as is found in an inverted duodenum; 3, subhepatic abscess; 4, emphysematous cholecystitis. These conditions are ordinarily easily eliminated by the proper special type of examination.

Conclusions. 1. A medical type of localized, spontaneous, sealed-off pinpoint perforation as a complication of duodenal ulceration is described.

2. The possibility of a sealed-off pin-

point type of perforation of a duodenal ulcer should be looked for in all recurrent ambulatory cases presenting symptoms which are more severe or unusual.

3. The incidence of this variety of walled-off perforation is probably greater than has been suspected.

4. In this form of perforation a small gas-bubble in the subhepatic area above and outside of the duodenal contour may be recognized.

5. It is generally associated with a recurrent active duodenal ulcer with a demonstrable niche defect.

6. The air-pocket frequently contains a small amount of exudate or fluid. No barium entered the pocket in the cases presented.

7. The subhepatic gas-bubble is best demonstrated on spot films in the erect position, utilizing the compression technique.

8. Five cases are presented, of walled-off sealed pinpoint type of perforation occurring in recurrent chronic duodenal ulceration. One of these was surgically explored and proved to have had a perforation.

REFERENCES

1. **Singer, H. A.**, and **Vaughan, R. T.**: Surg. Gyn. Obst., **50**, 10, 1930.

CO-EXISTENT HODGKIN'S DISEASE AND KAPOSI'S SARCOMA

Report of a Case with Unusual Clinical Features

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This case of Hodgkin's Disease is presented because of: a) the co-existence of Kaposi's Sarcoma, a rare and apparently unreported occurrence, and b) certain unusual clinical features.

Case Report. M. P., a 54 year old white male, was first seen by one of us (RHG) on October 18, 1946. He had been on a reducing diet for 1 year, but despite stopping the diet had continued to lose weight for 2 months, and felt weak. On examination, his weight was 182 pounds, the blood pressure was 150/80, the heart and lungs showed nothing noteworthy and a large, left upper quadrant abdominal mass was felt and thought to be spleen. No enlarged lymph nodes were palpated. The following day he was admitted to the hospital for diagnostic study. The physical examination showed no additional findings. The following laboratory studies were obtained: Hemoglobin, 10.7 gm. (74%); red cell count, 3,690,000; white cell count, 4,000 (62% segmented neutrophils, 6% non-segmented neutrophils, 25% lymphocytes, 4% monocytes and 3% young forms); platelet count, 180,000; bleeding time, 2 minutes; coagulation time, 5 minutes; blood sugar 104 mg.%; blood urea nitrogen 13 mg.% prothrombin time 100%; Total proteins 5.9 gm.%; Blood uric acid 4.8 mg.%. A fragility test showed hemolysis beginning at 0.44 and complete at 0.32. An aspiration biopsy of the sternal marrow revealed no evidence of a leukemic process.

Roentgen studies of the chest, urinary tract, gall bladder, upper gastrointestinal tract, colon and long bones revealed only some evidences of gastritis and duodenitis and old tuberculous foci in the lungs. No mediastinal adenopathy was demonstrated. A urinalysis for Bence-Jones protein was negative. An adrenalin test did not produce abnormal cells in the peripheral blood.

Because of the mild anemia and weakness, a blood transfusion was given. A splenic puncture was contemplated, but not performed. The patient was discharged with a diagnosis of "Splenomegaly of undetermined origin," and seen subsequently as an out-patient. In December, 1946, Roentgen therapy to the spleen resulted in a decrease in size of that organ and a rise in hemoglobin to 94%. The following month, a few enlarged cervical lymph nodes were noted. From a biopsy of one of these (Dr. David R. Meranze) "Lymphoblastoma, probably Hodgkin's Disease" was diagnosed.

Beginning in March, 1947, the patient's disease process gradually became more active, establishing a need for blood transfusions and Roentgen therapy. This supportive therapy not being helpful, the patient was re-hospitalized in June, 1947. A high fever developed and the anemia and leukopenia became more severe. The white blood cell count varied from 1200 to 2000 with 5 to 15% neutrophils. He developed gingival and rectal ulcerations. The rectal lesions progressed to an abscess which required incision. These lesions were kept under some control with penicillin and streptomycin. The anemia, however, was unrelieved by numerous transfusions.

At this time (July, 1947), despite the extreme neutropenia, nitrogen mustard therapy was instituted (20 mg. in 4 days). The response was dramatic, with an immediate subsidence of fever. The mucosal lesions healed rapidly, although no change was noted in the white cell count. Blood transfusions were now effective in bringing his hemoglobin and erythrocyte count to a more tolerable level.

During this admission, he first began to complain of pain in his toes and feet. An infiltrative skin lesion was noted, consisting of erythematous scaling papules involving predominantly the toes and the tibial crests. This lesion was not affected by the nitrogen mustard therapy—the lesions and associated pain

remaining, although the general symptomatology was markedly improved by the drug. No skin biopsy was taken. The clinical impression was that of either Hodgkin's cutaneous infiltration or Kaposi's Sarcoma.

From July, 1947, until his death on February 23, 1948, the patient received 5 courses of nitrogen mustard therapy, and numerous blood transfusions. During each remission, which lasted on an average of 4 to 5 weeks, there was disappearance of fever, improved appetite, and a rise in the hemoglobin level.

In September, 1947, an interesting hematologic development was noted. The white cell count, which had previously averaged 2000, rose suddenly to 6000 and then to 10,000. At that time there appeared in the peripheral blood many primitive cells of the monocytic type, numbering 60 to 70% of the total white cell count. Within a few days the numbers of these cells diminished rapidly and the leukocyte count dropped to 3000. Death occurred on February 23, 1948, during the eleventh hospital admission.

Autopsy (9 hours after death). The body appeared moderately emaciated, with slight cyanosis and scleral icterus. There was abdominal distension, with moderate edema of the legs and ankles. The toes, feet and pretibial regions showed the presence of numerous raised, flat, greyish-purple nodules, averaging 4 to 7 mm. in diameter and 1 to 2 mm. in height. Many of these showed a tendency to confluence and most showed slight scaling. The superficial lymph nodes were not palpably enlarged.

There was a left pleural effusion of 1200 cc. and 7200 cc. of fluid in the abdominal cavity. Marked perisplenic adhesions were present. A mass of conglomerate lymph nodes, varying from 1.0 to 3.5 cm. in diameter was present in the right anterior superior mediastinum. A mass of similar nodes was noted at the right lung hilum. The lungs showed moderate edema and congestion, with small foci of bronchopneumonia. Numerous small subpleural nodules, less than 1.0 cm. in diameter, were present. An old, fibro-calcareous lesion (tuberculous) was noted at the right lung apex.

The heart weighed 330 gm., was slightly dilated and showed slight coronary sclerosis. The gastrointestinal tract was essentially negative. The mesenteric lymph nodes were slightly enlarged. The liver was moderately enlarged, weighing 2550 gm., and showed alternate areas of swollen and collapsed lobules, with small hemorrhagic foci. There was slight cholesterolosis of the gall bladder mucosa.

The spleen was markedly enlarged, weighing 2120 gm. and measuring 28.0 x 18.0 x 9.0 cm. The capsule showed irregular areas of thickening, beneath which were seen large, sharply-demarcated, yellowish-grey infarcts. The pulp was soft, dark-red and mottled. The central areas were slightly diffluent, probably due to incomplete fixation.

The kidneys were slightly enlarged, having a combined weight of 440 gm. They showed slight surface granularity, with small superficial retention cysts. The pancreas, adrenals, urinary bladder, prostate and testes were not remarkable. The brain was not examined.

Histologic examination revealed extensive Hodgkin's lesions, involving the spleen, lymph nodes, sternal, rib and vertebral marrow and with small pulmonary and renal infiltrations. In addition, the bone marrow showed an essentially normal cellularity, with apparently normal maturation processes of the myelogenous and erythroid elements. Sections of the skin lesions revealed neoplastic areas in the corium consisting of small, irregular blood vessels in a reticular and fibroblastic framework. Erythrocytes were present in the vessels. Similar lesions were noted in areas of the lung, isolated from the Hodgkin's lesions, and in a few lymph nodes. These secondary lesions showed a marked tendency to produce a more fibroblastic picture. Large angiomatous spaces were also seen in the spleen in the vicinity of the infarcts. However, these were considered to be peculiar reactive changes rather than neoplastic. The liver showed an extensive subacute necrotizing hepatitis.

The *pathologic diagnoses* were: 1) Hodgkin's sarcoma of spleen, lymph nodes and bone marrow, with pulmonary and renal infiltrations; 2) cutaneous angio-endothelioma (Kaposi's sarcoma), with lymph node and pulmonary metastases; 3) massive ascites; 4) necrotizing subacute hepatitis; 5) cardiac failure with pulmonary edema and congestion; 6) terminal bronchopneumonia.

Comment. This case offers several avenues for discussion, from both the pathologic and the clinical viewpoints. Although a number of instances have been cited of the co-existence of Kaposi's sarcoma and leukemia[1,2,3] or lymphoblastoma[4], we have found no cases reported in which there was present Hodgkin's disease and Kaposi's sarcoma. Our review was based on the Quarterly Cumulative Index Medicus as a source of reference. Such cases, to be sure, have been seen, according to

Erf[5] and Wolf (in a discussion of a case presentation by Rosen[1]).

If we are to consider these 2 lesions (Hodgkin's disease and Kaposi's sarcoma) as being primarily of reticuloendothelial origin, their association should not be coincidental. Numerous workers (reviewed by Custer and Bernhard[6]) have commented upon the interrelationship of Hodgkin's disease, the other lymphoblastomas and their variants and leukemia, and the appearance of one or another of the lymphoblastomas in successive examinations in the same patient has been frequently noted. Willis[7] suggests that Kaposi's sarcoma may be a variant of the lymphoblastomas, with prominent skin lesions related to those of Hodgkin's disease and mycosis fungoides. However,

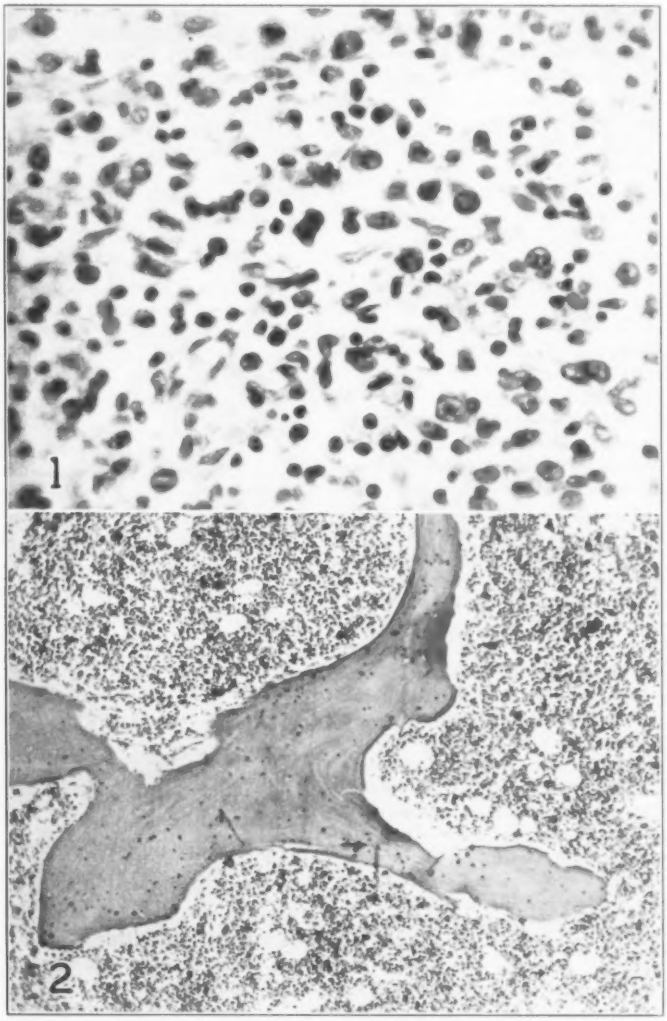

FIG. 1. Lymph node. Hodgkin's Disease (x 650).
FIG. 2. Bone Marrow (vertebral). Normal area (x 90).

Aegerter and Peale[8] feel that Kaposi's sarcoma originates in the angioblasts, and that this condition is a variant of angiosarcoma.

On the other hand, Symmers[9] regards Kaposi's sarcoma as a type of fibrosarcoma in which the seeming vascular spaces are pseudo-sinusoids and the erythrocytes are extravasated into these spaces from nearby capillaries by trauma. According to this opinion, the co-existence of Hodgkin's disease and Kaposi's sarcoma should be interpreted as an unrelated coincidence.

It is our belief that the two conditions present in the case reported are histogenetically related and that possible other coincident occurrences of these 2 lesions have not been fully appreciated and recorded.

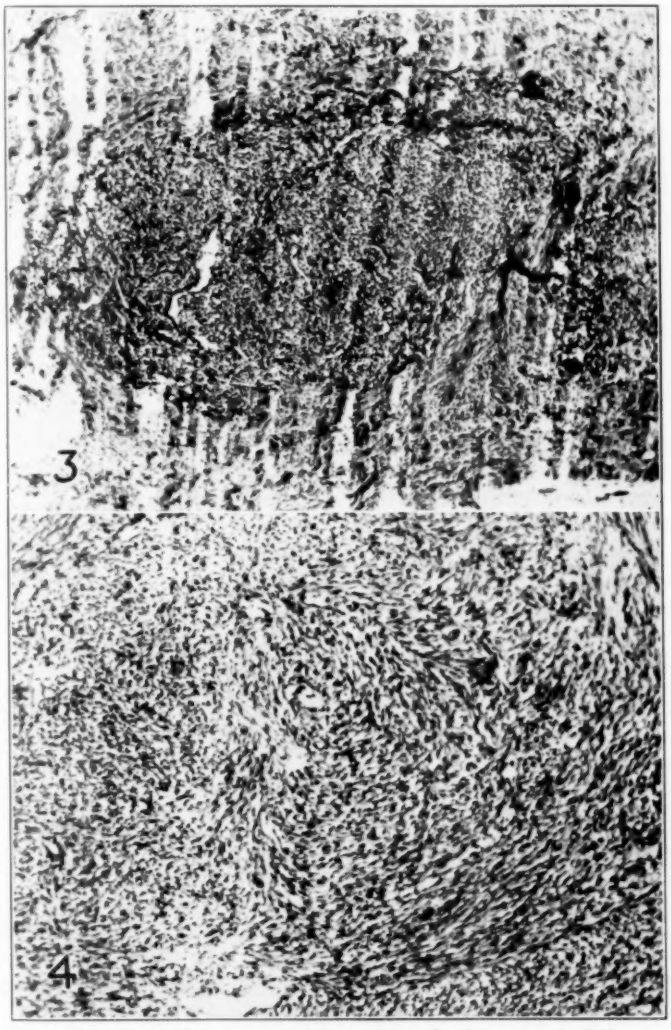

FIG. 3. Subcutaneous tissue. Kaposi's Sarcoma (x 75).
FIG. 4. Lymph node. Kaposi's Sarcoma (x 150).

In considering briefly the kindred nature of the lymphoblastomas, leukemia and Hodgkin's disease, it might be interesting to comment on one of the clinical features of this case. We refer to the transient rise in total leukocyte count (to 10,000 cells per c. mm.) with the appearance in the peripheral blood of large numbers (60 to 70%) of primitive mononuclear cells. These cells were similar to those noted in small numbers in the blood at the time of the first admission, and also to cells noted in the vascular spaces of the lymph node taken at the original biopsy. These cells probably arose from the reticulo-endothelial system, being released into the blood stream from active foci of Hodgkin's disease. This temporary abnormal leukocytosis, if viewed as an isolated finding in a patient with splenomegaly, could be diagnosed as leukemia. Custer and Bernhard[6] have reported various transition stages histologically between Hodgkin's or reticulum cell sarcoma and monocytic leukemia. It is only the changing clinico-pathologic picture which reveals the true diagnosis.

Finally, it is felt that some comment should be made upon the use of nitrogen mustard in this case. Although it is known to induce remissions in Hodgkin's disease, use of this drug has also resulted in severe depressions of the cellular elements of the bone marrow. Therefore its use where leukopenia is present should be regarded as fraught with danger. Despite a leukocyte count averaging 1000 to 2000 with marked neutropenia, however, and with full realization of the dangers, therapeutic dosage of nitrogen mustard therapy was attained. This resulted in no change in the leukopenia but produced dramatic clinical improvement, including healing of the agranulocytic mucosal lesions. This would suggest that this drug might be tried in a susceptible disease process even in the face of a marked leukopenia.

Summary. 1. A case of co-existent Hodgkin's disease and Kaposi's sarcoma is presented, no previous case having been found by us in an extensive search of the literature.

2. The possible relationship of these 2 disease processes, together with the lymphoblastomas and leukemias, is briefly commented upon.

3. The use of nitrogen mustard therapy in susceptible disease processes in the face of leukopenia is suggested.

REFERENCES

1. **Rosen, I.**: Arch. Dermat. and Syph., **48**, 566, 1943.
2. **Sachs, W.**, and **Gray, M.**: Arch. Dermat. and Syph., **51**, 325, 1945.
3. **Cole, H. N.**, and **Crump, E. S.**: Arch. Dermat. and Syph., **1**, 283, 1920.
4. **Lane, C. G.**, and **Greenwood, A. M.**: Arch. Dermat. and Syph., **27**, 643, 1933.
5. **Erf, L.**: Personal communication to R. H. G.
6. **Custer, R. P.**, and **Bernhard, W. G.**: Am. J. Med. Sci., **216**, 625, 1948.
7. **Willis, R. A.**: The Pathology of Tumours, p. 780, St. Louis, C. V. Mosby, 1938.
8. **Aegerter, E. E.**, and **Peale, A. R.**: Arch. Path., **34**, 413, 1942.
9. **Symmers, D.**: Arch. Path., **32**, 764, 1941.

THE MURMURS OF CARDIAC ANEURYSM

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The clinical diagnosis of ventricular aneurysms has depended chiefly upon roentgenological methods. In a small number a permanent bulging of the ventricular border is demonstrable in a chest film or by fluoroscopy. In a larger number of cases even careful examination fails to reveal any deformity of the cardiac border, although careful fluoroscopy or fluorocardiography may give evidence of a systolic expansion of the ventricular wall[5].

The antemortem diagnosis of a partial cardiac aneurysm can, however, be made in many cases on the basis of physical signs alone. For this reason the evaluation of any sign of diagnostic importance is worthwhile.

One of the most outstanding, though inconstant, findings is the presence of an abnormal cardiac pulsation in an unusual position; in most cases this is noted mesial and craniad to the area of the apex beat. The pulsation may appear within 6 days after a myocardial infarction[13] and soon reaches its maximum intensity. Sometimes it disappears as the connective tissue scar develops and shrinks, but ordinarily it persists for life.

Auscultatory signs of partial cardiac aneurysm were described early. A strong abnormal cardiac pulsation with weak peripheral pulses and distant heart sounds was considered to be a syndrome characteristic of a cardiac aneurysm[1,6]. In addition, gallop rhythm[11] and murmurs have been described. Aran[1,3] quotes Gendrin who found a "murmur double à temps séparés"; a dry ("sec"), sibilant systolic murmur was followed by a shorter, rougher ("rugueux") diastolic one. These murmurs could not be attributed to a mitral stenosis or to an insufficiency of the aortic valves. A systolic and a diastolic murmur were also reported by Paul[9] in a case of cardiac aneurysm. In a patient in whom the clinical diagnosis of a ventricular aneurysm was made, Remlinger[10] found a systolic and a diastolic musical murmur over a circumscribed area about 2 cm. above and lateral to the xiphoid process. These murmurs sounded as if an "ou" were followed by an "e". The murmurs gradually diminished in intensity, presumably because the aneurysm filled with thrombi. Autopsy revealed a partial cardiac aneurysm the size of a tangerine on the anterior wall of the left ventricle with a diameter of 5 cm. at the orifice. It was partly filled with layers of thrombi. Finally, Kasem-Beck[4], in a 63 year old man with a cardiac aneurysm the size of an apple above the apical area of the left ventricle, heard a presystolic murmur which, in combination with a dull first and an accentuated basal second sound, led to the wrong *intra vitam* diagnosis of mitral stenosis.

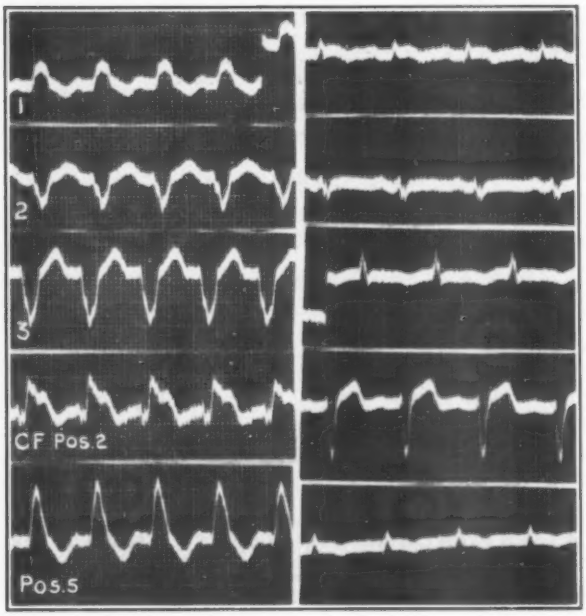


FIG. 1. CASE 1. Fig. 1a shows the electrocardiogram on admission; Fig. 1b was obtained 7 weeks later.

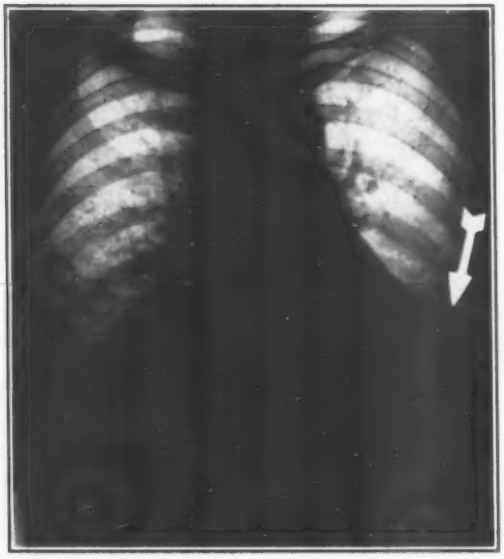


FIG. 2. Cardiac aneurysm on the left border.

In recent reviews[2,8] on the subject, dealing with a larger number of cases, the absence of abnormal murmurs is specifically mentioned. For this reason, and because these murmurs have not been registered with the stethogram, as far as we know, we decided to publish the following 3 recent personal observations. This seems particularly advisable since the presence of the diastolic murmur may lead to the erroneous diagnosis of other cardiac lesions, as will be pointed out later.

Case Reports. CASE 1: J.B., a 69 year old colored woman, experienced on April 20, 1948, severe epigastric pain which was constant, dull, and of great intensity. It was accompanied by vomiting, and lasted for 5 hours until an injection of morphine brought relief. The blood pressure fell from 132/90 to 80/60. The white cell count was 10,500; the temperature rose no higher than 99.9°. In the past history the existence of a chronic duodenal ulcer was related. The patient acknowledged syphilis in her youth, and had received some treatment. The serological reactions during the period of obervation were consistently negative. The heart sounds were always loud and pure.

The electrocardiograms obtained on admission showed (Fig. 1a) in the standard leads, the pattern of a left bundle branch block, without any other abnormalities. In the chest lead from position 2 (CF lead) there was, however, a distinct high take-off preceded by a wide and notched Q wave, proving the presence of a new anterior wall infarction. The chest lead in position 5 showed only the delay of the intrinsic wave over the left ventricle, which is characteristic of a left bundle branch block. An electrocardiogram obtained on June 11, 1948 (Fig. 1b) showed that the bundle branch block had disappeared. The QRS complexes were slurred without being widened and the voltage was low. There was, in addition, a high take-off of the RST segment in Lead 1, followed by a slight inversion of the T-wave. The R-wave was very low in position 2 and also in position 5 of the chest leads. In the latter lead an inverted T-wave is visible.

On June 9, 1948, a precordial pulsation was first noted above and inside the apical region. It impressed one as a small hemispheric bulge, a little more than 1 inch in diameter. A faint systolic and a diastolic gushing, high-pitched murmur were audible only over the pulsation. These murmurs persisted until the patient was discharged in July, 1948. A chest plate on June 15th showed an aneurysmal bulge on the lower left cardiac border (Fig. 2). A stethogram (Fig. 3) was taken at the same time over the pulsation with a Cambridge unit. It revealed, in addition to a prolonged and occasionally split

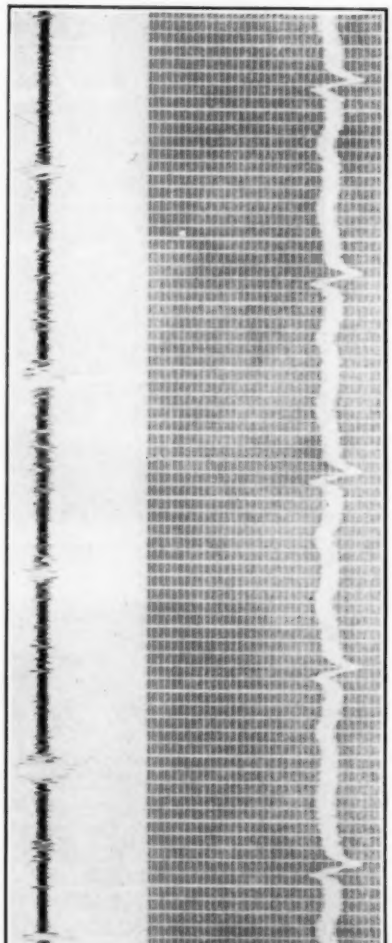
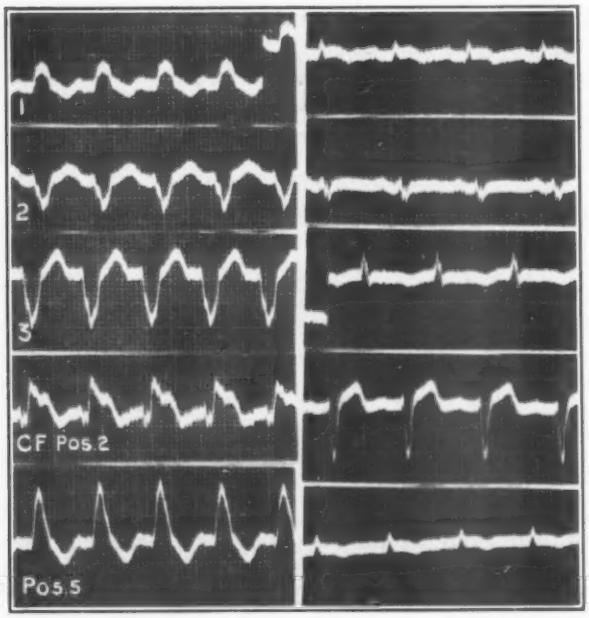


FIG. 3. Stethogram, taken over the pulsation in Case 1.



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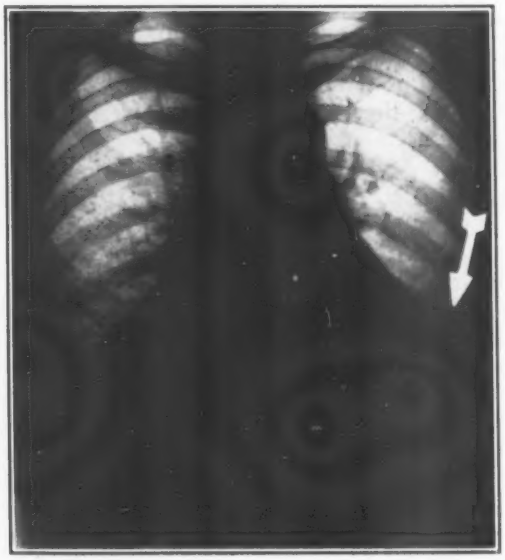

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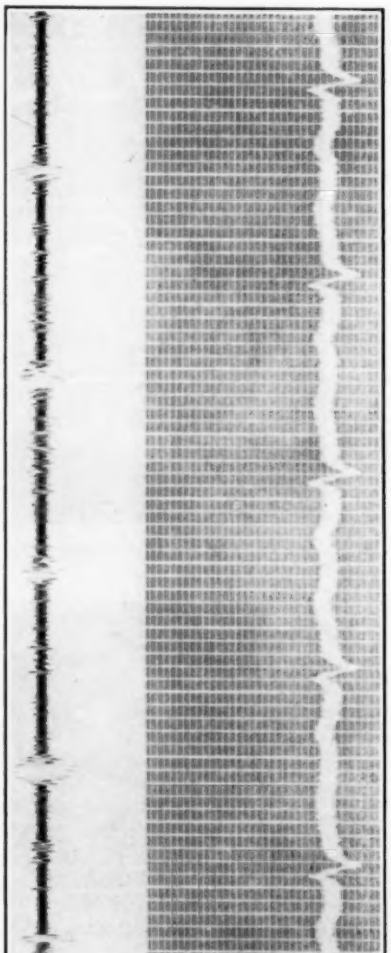

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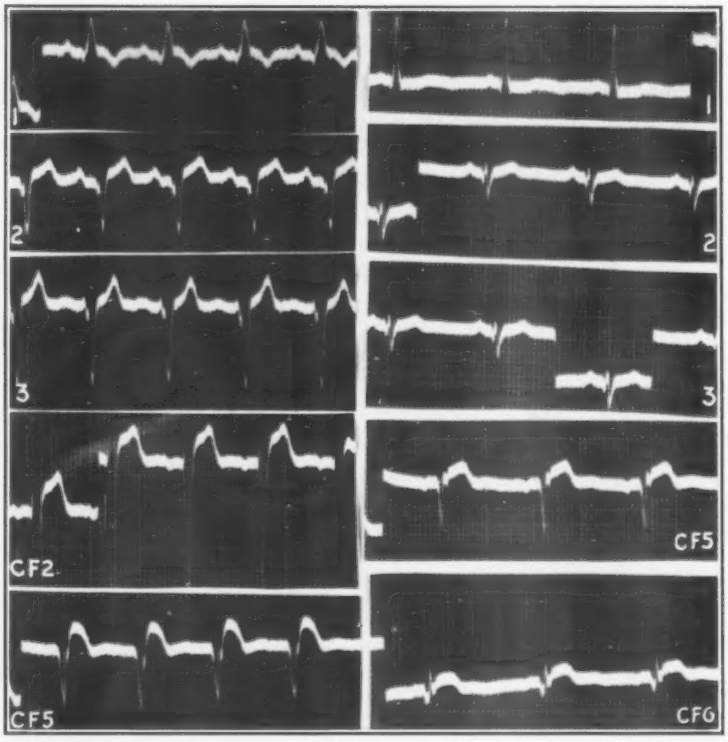

FIG. 4. CASE 2. Fig. 4a was obtained on the day after admission; Fig. 4b about 2 mos. later.

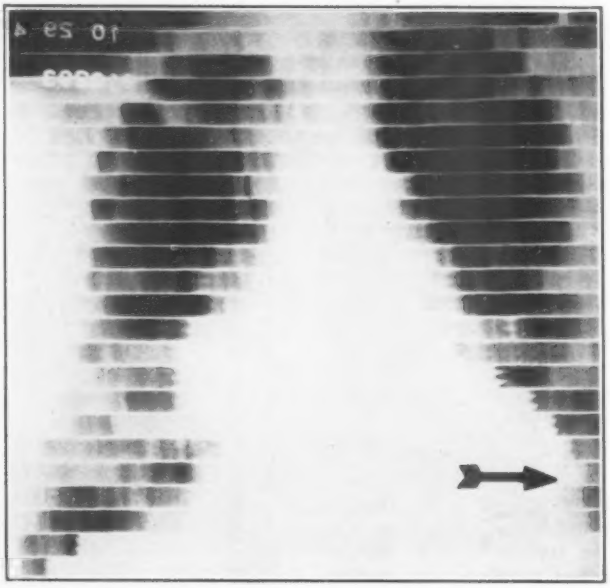

FIG. 5. Absence of pulsations in the kymogram of the left lower cardiac border.

second sound, a faint systolic and a prolonged diastolic murmur. The systolic murmur in most of the cycles had an increased amplitude of vibrations toward the end of the systole and, at times, fused with the vibrations of the second sound. The diastolic murmur filled all diastole and in some cycles was louder toward the end of diastole. The auricular contraction was accompanied by an increased intensity of this murmur. Over the rest of the heart, only pure sounds were recorded.

The patient died suddenly at home in September, 1948.

CASE 2: M.J., a 64 year old man, had been hospitalized 2 years before his attack of myocardial infarction for hypertension (170/110) and congestive heart failure. At that time, the increase of blood pressure had already been known for 5 years. The gall bladder had been removed in 1941 because of cholecystitis. The patient was readmitted on September 17, 1947, because of a continuous, sharp, constricting pain in the lower and mid-substernal regions, which radiated down both arms and up towards the neck. The pain began at midnight prior to admission and it waxed and waned until the patient entered the hospital. Associated symptoms were dyspnea, cold sweats, and nausea. The pressure fell to 128/96, the sedimentation rate rose to 85 mm.; the urea nitrogen rose temporarily to 37.5 mg. and the temperature to 101.1°. The white cell count was 14,250. There was no history of previous syphilis and the serological tests were repeatedly negative. The heart sounds were distant and pure. A protodiastolic gallop rhythm was heard during the first few days after admission.

The first electrocardiogram which was ob-

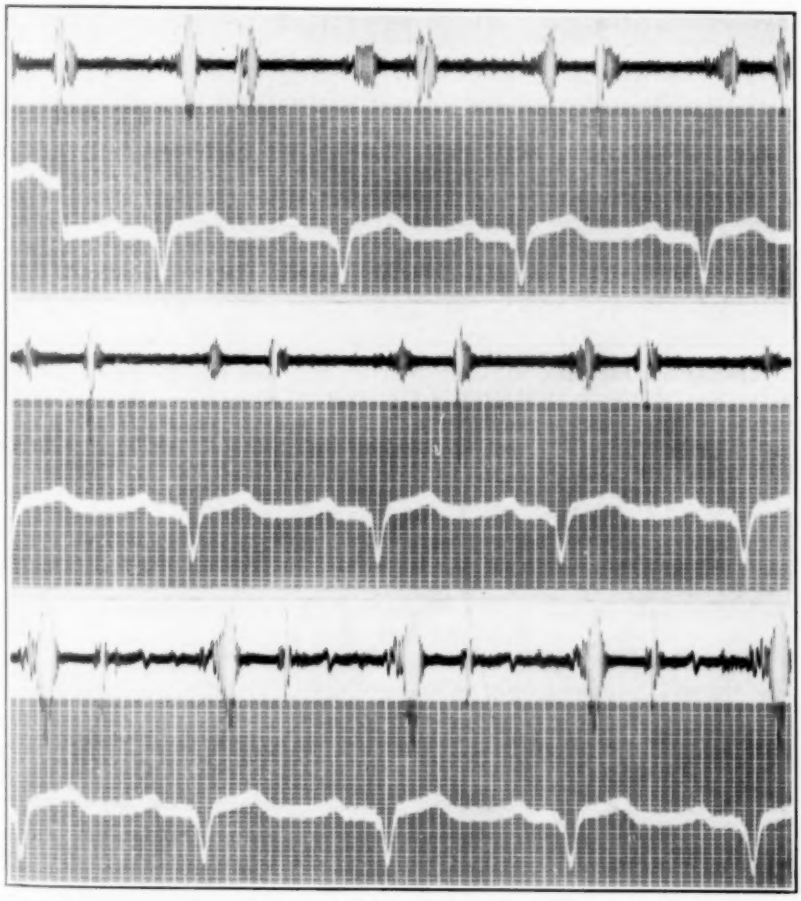

FIG. 6. Stethograms from the aorta (a), the pulmonary artery (b) and the apex (c).

tained on September 18th, the day after admission (Fig. 4a), showed left axis deviation in the standard leads, with a widening of the QRS complexes to 0.12 second, and a slight elevation of the RST-segments in Lead 1. In CF-5 the R-wave was absent, and the ST-segment was abnormally elevated. A second electrocardiogram, recorded on November 11, 1947, (Fig. 4b) showed left axis deviation with less widening of the QRS-complexes (0.10 second), and an abnormally low T-wave in Lead 1. The elevation of the RST-segment in the chest leads, particularly in the CF-5 and CF-6, is abnormal.

A chest plate, taken on October 30, 1947, showed a plump heart, with an apparently obviously enlarged left ventricle, without circumscribed bulging, a finding which is com-

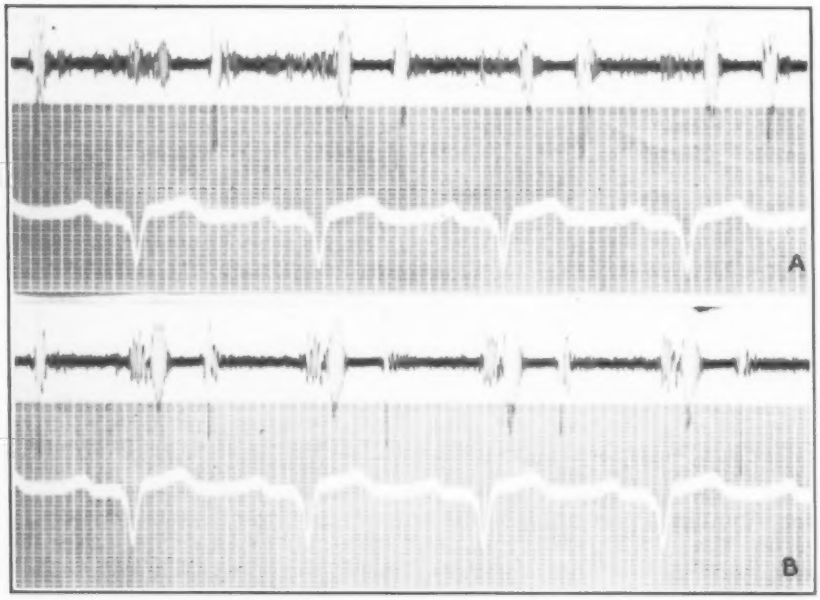

FIG. 7. Stethograms from the pulsating aneurysm (a), and the 4th intercoastal space, to the left of the sternum (b).

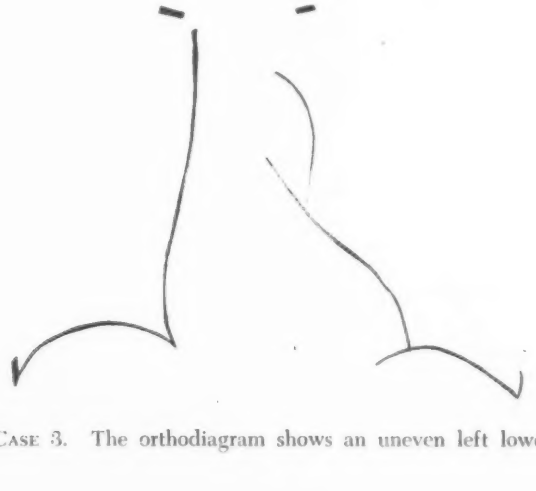

FIG. 8. CASE 3. The orthodiagram shows an uneven left lower border.

mon in cardiac aneurysms. A kymographic study showed absence of pulsations on the lower left cardiac border (Fig. 5).

On October 1, abnormal pulsations over the same area as in Case 1 were observed for the first time; simultaneously, very loud systolic and diastolic murmurs were heard over the same region. During the following days the murmur became louder and reached its maximum intensity by mid-October.

A series of stethograms was taken on October 8, 1947. Over the aorta (Fig. 6a) the first sound is prolonged; the second sound is also prolonged and occasionally split. In some cycles there is a late systolic murmur, fusing with the vibrations of the second sound. Pure sounds were registered over the pulmonary artery (Fig. 6b) while a third sound and an auricular sound were recorded over the apex (Fig. 6c).

A loud diastolic murmur was registered over the pulsation of the aneurysm (Fig. 7a). It was continuous but increased in presystole. The murmur merged with the first heart sound. Slightly mesial to the area of the pulsation, over the 4th intercostal space, just to the left of the sternum, the diastolic murmur was still present, although diminished in intensity (Fig. 7b). The splitting of the first sound was probably related to the intraventricular block.

On October 5, 1947, the patient suddenly developed severe pain in the right upper quadrant of the abdomen, with marked dyspnea, orthopnea and sweating. The left leg became cold and there was severe pain. The blood pressure was 130/100. The patient was given oxygen, papaverine, aminophylline and morphine. Peripheral vein thrombosis and pulmonary embolism were diagnosed. The patient recovered from this episode and continued to improve. He was discharged on November 12, 1947. He died suddenly in January, 1948.

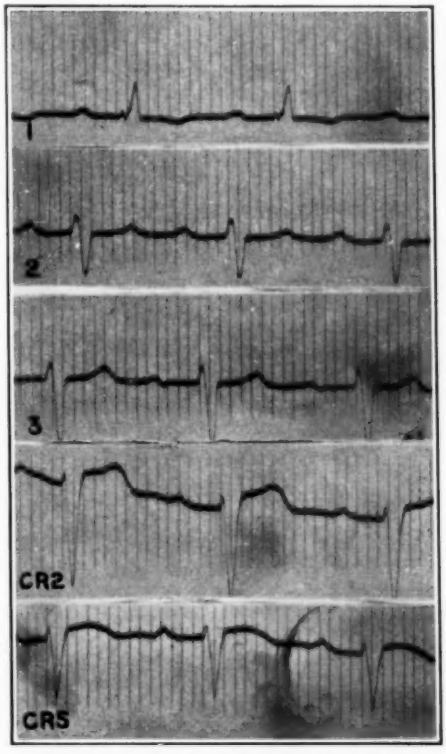

FIG. 9. Electrocardiogram of Case 3, showing in the chest leads an abnormally low R-wave and an elevated S-T and T.

CASE 3: L.K., a 65 year old man, came under observation with a history of a myo-

cardial infarction which had occurred 2 years earlier. For 5 weeks prior to admission, the patient suffered from nocturnal dyspnea. The heart was enlarged to the left and its left lower border was clearly uneven on fluoroscopy. Fig. 8 shows the orthodiagram. A protodiastolic gallop rhythm was audible over the apical area. A systolic pulsation extended to the midclavicular line about 2 inches inside the apical area. Distinct systolic and diastolic murmurs were heard constantly over the pulsation for an observation period of more than 1 year. There was no history of and no findings due to a syphilitic infection. The blood pressure was 180/130 on the first examination and after compensation with digitalis it fell to 140/100.

The electrocardiogram showed a P-R interval of 0.24 second (Fig. 9). There was a left axis deviation with inverted T-waves in Lead 1. The CR-2 lead was normal, whereas in CR-5 the R-wave was abnormally low and the RST-segment was abnormally elevated. The stethogram showed normal sounds over the apex and the aorta and a long diastolic murmur, lasting throughout diastole over the pulsation of the aneurysm (Fig. 10). In this case as well the murmur was definitely accentuated toward the end of diastole.

Discussion. All 3 cases undoubtedly had sustained a myocardial infarction. This is proved by the typical clinical syndrome and by classical electrocardiograms, indicating the presence of a large transmural infarction of the anterolateral wall of the left ventricle. The absence of an R-wave in the chest leads over the lateral wall of the left ventricle cannot be interpreted otherwise.

The patients show a persistent elevation of the RST-segment in Lead I and particularly in the chest leads taken over the infarcted area[7,12]. This finding, which is common in transmural, "through and through" infarctions, is often misleading and makes the examining physician diagnose a fresh infarction. Since in patients with large transmural infarctions, aneurysms often develop, this electrocardiographic pattern is common in cardiac aneurysms of the anterolateral wall of the left ventricle.

All cases had roentgenologic findings of a cardiac aneurysm and circumscribed bulging pulsations inside and above the apex area. In all cases systolic and diastolic murmurs were heard over this pulsation. The systolic murmur was somewhat rough and short. The diastolic one was high-pitched, gushing and soft; in all (or most) par-

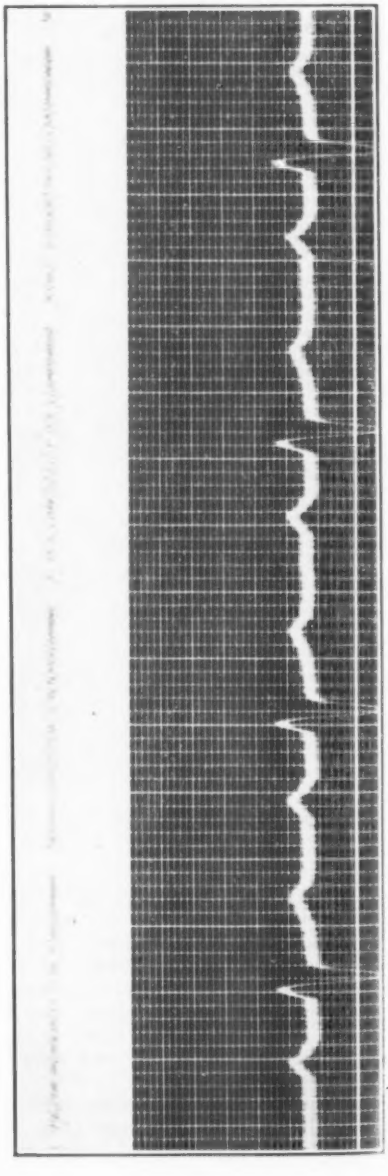

Fig. 10. Stethogram of Case 3.

ticulars it resembled the murmur heard in aortic regurgitation.

The last named lesion, insufficiency of the aortic valves, may easily be confused with a cardiac aneurysm because of the close resemblance of the murmurs. It is well known that in patients with insufficiency of the aortic valves particularly of rheumatic origin, the murmur is also heard on the left lower sternal border, very close to the site at which the murmur of the cardiac aneurysm usually is found. Actually, in 4 cases, one of us made the diagnosis of an aortic insufficiency despite the absence of its other signs, and yet autopsy revealed the presence of a cardiac aneurysm. This led us to pay particular attention to the auscultatory findings in this lesion. In the cases described in this paper, the absence of other signs of an aortic lesion, the presence of the murmur only over the left lower sternal border, and (as in Cases 1 and 2) its absence until some time after the occurrence of the myocardial infarction, made us rule out a lesion of the aortic valves due to a marked dilatation of the left ventricle. In one case of cardiac aneurysm described by Strandell, a diastolic murmur was heard, but autopsy revealed very rigid, calcified aortic valves.

For the differentiation between a diastolic murmur due to an insufficiency of the aortic valves and that of a cardiac aneurysm, the stethogram is of help. The vibrations due to an aortic regurgitation are very high-pitched and have their maximum intensity either immediately after the second sound or at the time of the rapid filling in early diastole; those recorded in our cases of aneurysm were present throughout diastole and experienced an increase in presystole.

In addition to the diastolic murmur of an aortic regurgitation two other phenomena must be differentiated. One is a gallop rhythm or a diastolic third heart sound which often simulates a diastolic murmur. The roughness and evanescence of these extra sounds should make a distinction relatively easy, even without a stethogram. The second is a pericardial friction rub which may have two causes. One is due to dilatation of the heart *per se*. There is no doubt that even with a normal pericardium, dilatation of the left ventricle alone, particularly in children or in a person with a small chest, and even more often when the left lateral recumbent position is assumed, causes a fine, silky friction rub to appear. Presumably this is due to the friction between normal epi- and pericardium. This friction rub usually can be recognized by its auscultatory qualities and by its dependence on the phase of the respiration. In rare cases a permanent friction rub is heard in patients whose earlier pericarditis caused thickening and roughening of the pericardium without leading to an obliteration of the pericardial cavity. This phenomenon too causes vibrations which are recognized by auscultation alone.

To explain the origin of the aneurysmal murmur is difficult. It was believed that the passage of blood into the orifice of the aneurysm, which often is narrower than the largest diameter of the aneurysmal sac, causes the murmur[3]. Our findings, which show that the murmur is louder towards the end of diastole, speak somewhat against this conception unless one assumes that the auricular contraction forces blood with still greater force into the aneurysm and causes a turbulence of blood with formation of whirlpools. However, it must be assumed that the amount of residual blood in the left ventricle is greater than usual and that the aneurysmal sack is not empty at the beginning of diastole. If one assumes that the blood is forced into the aneurysmal sack during systole to cause the systolic pulsation and the systolic

murmur, and that the diastolic backflow of blood into the left ventricle causes the diastolic murmur[15], it is difficult to understand why the murmur should be louder at the end of diastole.

Conclusions. In 3 cases of cardiac aneurysm due to myocardial infarction a diastolic murmur has been registered over the aneurysm with the stethogram. The murmur is loudest towards the end of diastole. The mechanism of origin of this murmur is discussed. These patients have a large transmural infarction which causes permanent displacement of the RST-segment otherwise seen only in the acute phase of a myocardial infarction.

REFERENCES

1. **Aran, F. A.:** Union Med. **11**, 479, 1857, and Bull. Soc. med. d. hôp. de Paris, **3**, 445, 1864.
2. **Dressler, W.,** and **Pfeiffer, R.:** Ann. Int. Med., **14**, 100, 1940.
3. **Huchard, H.:** Traité clinique des maladies du coeur, 3d vol., 3d ed. Paris 1899-1903.
4. **Kasem-Beck, A.:** Centralbl. f. inn. Med., **18**, 137, 1897.
5. **Luisada, A. A.,** and **Fleischner, F. G.:** Acta Cardiol., **4**, 308, 1948.
6. **Lutembacher, R.:** Arch. d. mal. du coeur, **13**, 49, 1920.
7. **Nordenfelt, O.:** Acta med. Scand., **102**, 101, 1939.
8. **Parkinson, J., Bedford, D. E.,** and **Thomson, W. A. R.:** Quart. J. Med., **7**, 455, 1938.
9. **Paul, C.:** Bull. et mem. Soc. med. d. hôp. de Paris, 3d s. **2**, 83, 1885.
10. **Remlinger, P.:** Bull. med. Paris, **10**, 483, 1896.
11. **Rendu, H.:** Bull. et. mem. Soc. med. d. hôp. de Paris, 3d s. **4**, 455, 1887.
12. **Scherf, D.,** and **Boyd, L. J.:** Med. Clin. N. Am., **26**, 919, 1942.
13. **Scherf, D.,** and **Erlsbacher, O.:** Med. Klin., **30**, 1687, 1934.
14. **Strandell, B.:** Acta med. Scand., **74**, 148, 1930.
15. **Strauch: Ztschr.** f. klin. Med., **41**, 231, 1900.

CONGENITAL POLYCYSTIC DISEASE OF THE KIDNEY: REVIEW OF THE LITERATURE, AND DATA ON 207 CASES

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The remarkable and not infrequent affliction of the kidneys known as polycystic disease has been recognized for several centuries but its pathogenesis has yet to be delineated. The numerous theories advanced as to its etiology may be conveniently described under the categories of metabolic, inflammatory, neoplastic, and developmental defects.

Etiology. Virchow[34] first suggested, on the basis of microscopic observations, that structural changes in the kidneys in this condition were due to deposition of salts in the renal tubules with resultant tubular obstruction followed by formation of cysts. Subsequently Virchow[35] suggested that papillitis or pyelitis in fetal life might cause tubular fibrosis, obstruction and cystic change. Ribbert[27] also suggested nonspecific inflammatory changes during fetal life as the cause of the cystic changes but concluded that their effect was to prevent union of the uriniferous and collecting tubules. Numerous writers[30,32] have suggested fetal syphilis as the cause of the tubular obstruction.

Histologically many polycystic kidneys present the picture of vigorously growing tumors and only recently Staemmler[31] has applied the term "cystadenofibroma" to these changes. Brigidi and Severi[5], however, were the first to suggest that polycystic disease of the kidney represents a true neoplastic process.

Since Kupffer[15] first demonstrated that the adult kidney is derived from two separate anlagen, there has been much speculation concerning how this peculiar process may influence the development of polycystic kidneys. Embryologically, the adult kidney is derived from the metanephros which forms the ureter and a series of 12 to 14 generations of buds from it which form the collecting tubules. The glomerulus, convoluted tubules and loop of Henle are formed from a condensation of mesenchyme overlying the budding metanephros and termed the "metanephric blastema"[14]. From his microscopic studies, Mutach[21] came to the conclusion that the cysts resulted from cessation of growth of the developing renal anlagen before union of the uriniferous and collecting tubules. Kampmeier[13], and McKenna and Kampmeier[18], as a result of careful reconstructions of serial sections of fetal kidneys and in 1 case of polycystic kidneys, were of the opinion that the fundamental defect in a polycystic kidney was failure of the 2nd to 4th generations of uriniferous tubules to atrophy. They found that these generations of uriniferous tubules joined with similar generations of collecting tubules but later (about the 3rd month of fetal life) separated and remained for about a month as cystic tubules. Kampmeier[13] was able to demonstrate as many as 40

of these cystic tubules in each kidney of normal fetuses 3 months of age. A few weeks later these tubules either atrophied or united with the 5th or later generations of collecting tubules. Polycystic kidneys, then, might represent a failure of atrophy of these particular generations of uriniferous tubules. More recently Norris and Herman[23], on the basis of reconstructions of serial sections in 2 cases of infantile polycystic kidney and 2 cases of adult polycystic kidney disease, elaborated on Kampmeier's theory. They pointed out that many of the cysts undoubtedly are derived not only from uriniferous tubules but also from collecting tubules as noted by Forssman[9]. Also they found that there were anastomoses between the cysts in both prenatal and postnatal kidneys. They suggested that in polycystic disease of the kidney a much greater portion of the metanephros than normal is provisional and that during fetal life rapid growth and anastomosis of these collecting and uriniferous tubule cysts occur so that when these fail to atrophy, polycystic kidneys result. Moolten[19], on the basis of histologic studies, has suggested that the primary defect is one of organizer action rather than one of cell competence. He regarded congenital polycystic disease of the kidney as a disseminated hamartosis similar to tuberous sclerosis and Lindau's disease.

In contrast to the multitude of theories, the amount of experimental work reported on which these theories have been based is small indeed. The foundation for these theories has been simple microscopic anatomy and, in some instances, reconstructions of serial sections. Petterson[26] and Tollens[33], working independently, first investigated the results of renal tubular occlusion. Utilizing the rabbit, they cauterized or ligated the renal papillae and noted first a dilatation of the tubules followed shortly by atrophy and obliteration of the epithelium and ending in a small contracted kidney which in no way resembled a polycystic kidney. These experiments, however, were not done on fetuses of rabbits, and it is possible that obstruction of the tubules of fetal animals would result in a different picture from that when the same procedure was carried out on the adult. Hepler[11], and Hinman and Hepler[12] studied the development of hydronephrosis in dogs produced by ureteral ligation and noted that simultaneous partial occlusion of the renal artery hastened the development of the hydronephrotic process. If only one branch of the renal artery is occluded and the ureter to that kidney is ligated, then cystic dilatation develops in the infarcted portion of the kidney. Apparently renal ischemia in the presence of ureteral obstruction produces more rapid cystic change. The cyst, however, originates from the renal pelvis and does not involve tubules derived from the uriniferous tubules as do the cysts in cases of congenital cystic kidney.

Ritter and Baehr[28] injected the arterial tree with barium gelatin in 5 cases of congenital polycystic kidney, made roentgenograms, and noted a gross diminution in the number and size of the arterioles. This observation was confirmed by Schacht[29] who made histologic measurements of the ratio of the diameter of the arterioles to the width of their walls. He noted a decrease in this ratio in all polycystic kidneys that he examined: that is, a decrease in the diameter of the lumen and an increase in the width of the wall. Schacht suggested this change as the cause of hypertension in polycystic disease of the kidney, whereas Ritter and Baehr advance the hypothesis that arteriolosclerosis is the cause of polycystic disease itself.

Bagg[1] has been the only one to produce a polycystic kidney experimentally. This was done by unfiltered

Roentgen irradiation of the abdomen of one generation of mice, and careful examination of all their descendants. Polycystic kidney, renal aplasia, horseshoe kidney and other congenital anomalies appeared in a certain percentage of the members of the 3rd and 4th generations. He found that the tendency to congenital renal anomalies was inherited as a Mendelian recessive. No attempt has been made to relate irradiation to the development of congenital polycystic renal disease in human beings, although with the increasing use of radioactive isotopes such work would be of considerable interest.

Thus, with this one exception, the mechanism of which is unknown, it has been impossible to produce polycystic disease of the kidney in the laboratory. The most tenable theory at present is the one first suggested by Felix[14], and later elaborated by Kampmeier[13], that the uriniferous tubules of certain generations fail to atrophy or reunite with the collecting tubules resulting in the presence of a functioning glomerulus with no means of excreting the urine formed and the consequent development of multiple glomerular and tubular cysts. Undoubtedly the development of associated renal arteriolosclerosis has a great influence on the progression of polycystic disease of the kidney.

PRESENT STUDY. The present report is based on study of 2 groups of cases; the first is composed of 207 cases of polycystic disease of the kidney seen at the Mayo Clinic from 1932 through 1947, and the second, of 46 cases of polycystic disease of the kidney in which complete necropsy data were obtained during the years 1920 through 1947. Of the patients in the first group 44 have been followed, usually by letter, until death, and 2 more have died and undergone necropsy at the clinic. The latter 2 have been included in the second group of 46 cases. Ninety-nine patients in the first group have been traced by letter or seen within the 12 months previous to August, 1948, and are still alive. We have been unable to trace 62 patients. In all cases the diagnosis has been verified by: 1, intravenous or retrograde pyelograms; 2, by examination of the kidneys at the time of operation or, 3, at necropsy.

DURATION OF LIFE. The age of the patients when they first registered at the clinic is given in Table 1. The average age at death was 49.3 years when those infants dying before the age of 6 months of the infantile variety of polycystic disease of the kidney were excluded (Table 2). As this whole series extends over a relatively short period of time relative to life expectancy (only 17 years have elapsed since the first patient came to the clinic), it might seem that those patients who have died thus far had, in general, the more severe types of polycystic disease of the kidney, and the average life expectancy should be corrected upward.

TABLE 1. AGE AT TIME OF DIAGNOSIS AT CLINIC AND SEX DISTRIBUTION

Age years and sex	Cases	%
0-9	6	3
10-19	2	1
20-29	18	9
30-39	71	34
40-49	56	27
50-59	41	20
60 or more	13	6
Total	207	100
Sex		
Males	94	45
Females	113	55
Total	207	100

TABLE 2. AVERAGE DURATION OF LIFE (EXCLUDING INFANTILE VARIETY)

	Traced patients	Average age, years
Patients first seen before 1943, still living	55	51.5
Patients who have died (excluding the infantile type of polycystic kidney)	85	49.3
Duration of life after onset of symptoms	43	9.3*
Duration of life after onset of azotemia	17	2.2*

* Duration in years after onset of symptoms.

Hence, the average age of all patients who were traced and found to be still alive 5 years or more after the diagnosis was made was determined. This was 51.5 years. Obviously the life expectancy of these patients is an indeterminate number of years greater than 51.5, yet they must be included with the previous group to form an accurate appraisal of the true life expectancy of a patient with polycystic disease of the kidney. So, although the life expectancy of the average patient with polycystic disease of the kidney cannot be determined exactly from these data, it must be somewhat more than 50 years. The necropsy data also suggest that many patients with this disease may live a normal life span, for it may be seen that 22% of the patients lived to be 60 years of age or older. Also, we are in correspondence with 2 patients, 84 years of age, who have polycystic disease of the kidney which was first diagnosed 16 and 10 years ago respectively and who are at this time in good health.

We were able to date the onset of symptoms of 43 patients with a reasonable degree of accuracy and follow them until death. The time interval averaged 9.3 years. The 17 patients for whom we could more or less accurately determine the onset of azotemia (as indicated by a concentration of urea in the blood of more than 40 mg. per 100 cc.) lived on the average of 2.2 years, and 1 patient lived 5½ years. This strikes a somewhat more optimistic note than some figures in the literature. Nolan[22] said, for example, that 50% of patients who have polycystic kidneys are dead 4 years after the diagnosis is made. Oppenheimer[24], however, has reported on a series of 60 patients whose average age at death was 50 years, and whose average age at the onset of symptoms was 41.5 years. Our data suggest that the evalution of any therapeutic procedure must be tempered by the fact that present conservative medical measures may result in a life expectancy after the onset of symptoms of almost 10 years for the average patient. In 199 of the 207 cases studied no specific treatment was suggested. In 8 cases, puncture of the cysts, the Rovsing procedure, was performed. This was done primarily for the relief of intractable pain.

Clinical Data. The sex distribution in our 207 cases was essentially the same as that reported by Braasch and Schacht[4] in 1932, which showed no predilection for either sex. In about a third of the patients we were able to elicit a family history of polycystic kidneys and, in a fourth more, a questionable familial history of the disease; for example, the mother and two brothers of 1 patient died of kidney disease (Table 3). The difficulty of examining all relatives of patients living at a distance from the clinic prevented accurate tracing of a sufficient number of families to establish the manner of inheritance of this condition. Bell[2] has expressed the opinion that polycystic kidneys are inherited as a Mendelian dominant although enough complete geneologies have not been made to establish this conclusively. We have referred previously to the observation of Bagg[1] that the descendants of irradiated mice inherited polycystic kidneys as a recessive tendency. Numerous instances of polycystic kidneys in families have been noted: 17 of 40 members of one family[6], 9 of 27 members of 4 generations in another[10], 5 children of the same mother[7], and 6 persons in 2 generations of the same

TABLE 3. FAMILY HISTORY OF POLYCYSTIC KIDNEY

Family history	Cases	%
Positive and definite	72	34
Questionable	55	27
Negative	80	39
Total	207	100

family[25] have had polycystic kidneys.

The main presenting complaints of our 207 patients at the time the diagnosis of polycystic kidneys was made are given in Table 4. The pain for

TABLE 4. CLINICAL DATA

Presenting complaint or findings	Cases	%
Presenting complaint		
Lumbar or abdominal pain	58	28
Presence of abdominal mass	42	20
Elevated blood pressure	35	17
Frequency, urgency or burning on urination	36	17
Painless hematuria	26	13
Hematuria and renal pain	21	10
Kidney failure (edema, uremia and so forth)	2	1
None related to kidneys	39	19
Findings on physical examination		
Elevated blood pressure (more than 140 mm. of Hg. systolic or 90 mm. diastolic)	146 (of 200)	73*
Palpable, enlarged kidney or kidneys	150 (of 207)	72†

* % of 200 cases in which blood pressure was recorded.
† % of 207 cases.

which about two-fifths of these patients came to the clinic had no definite pattern. It was located in the lumbar region or upper or lower part of the abdomen. It was usually nagging and dull, although attacks of colic were not uncommon. Colicky pain sometimes was associated with hematuria as a result of the ureteral spasm while blood clots were passed and in some cases it was an indication of associated renal calculi.

Of our 207 patients 20% came to the clinic because of the presence of an abdominal mass, discovered either by themselves or by their physicians. One-sixth of the patients came to the clinic because of the previous finding of high blood pressure. This further emphasized the frequent occurrence of hypertension in cases of polycystic disease of the kidneys, a point first noted by Braasch[3] in 1916. The rather large number (17%) of patients whose presenting complaints were of urinary frequency, urgency, burning or incontinence, emphasizes the frequency of renal and vesical infection in cases of polycystic kidneys. Sulfonamides, penicillin and streptomycin are of invaluable aid in the treatment of these common complications of polycystic disease of the kidney. The high incidence of painless hematuria in patients with this disease has been emphasized but is not entirely substantiated by our series since it was noted by less than 12% of our patients[16,17].

A blood pressure consistently higher than 140 mm. of mercury systolic or 90 mm. diastolic, in 73% of our cases is in accord with Braasch and Schacht's[4] observations. The fact that almost 72% of the patients on admission had palpable, enlarged kidneys (one or both) re-emphasizes the importance of this feature in the diagnosis of polycystic disease of the kidney.

The ocular fundi were examined in 105 of our 207 cases. In 71.5% changes typical of hypertension were noted, and, although an attempt was made to correlate these findings with the severity of the hypertension and the extent of renal failure (Table 5), no clear-cut evidence was obtained.

TABLE 5. CHANGES IN OCULAR FUNDI IN 105 CASES

	Ocular fundi (changes, grades 1 to 4*)				
Blood pressure	Normal	1	2	3	4
Normal (less than 140/90)	9	2	2		
Between 140/90 and 180/110	14	13	4		
More than 180/110	2	12	8	1	
Elevated blood pressure and elevated concentration of blood urea	5	21	9	1	2
Total	30	48	23	2	2

* Based on classification of Wagener, H. P., and Keith, N. M.: Diffuse Arteriolar Disease With Hypertension, and Associated Retinal Lesions. Medicine, **18**, 317, 1939.

The intravenous pyelogram usually presented a typical appearance. The calices were elongated and there was some blunting and irregularity of outline.

Albuminuria, pyuria, and somewhat less frequently, hematuria, were noted in most of the patients with polycystic disease of the kidney. The high incidence of pyuria (Table 6) suggests

TABLE 6. LABORATORY STUDIES

	Cases	%
Albuminuria		
None	46	22
Grade 1 to 2+	143	69
Grade 3 to 4+	18	9
Hematuria		
None	156	75
Grade 1 to 2+	33	16
Grade 3 to 4+	18	9
Pyuria		
None	64	31
Grade 1 to 2+	121	58
Grade 3 to 4+	22	11
Elevated value for blood urea (more than 40 mg. per 100 cc.)	72 (of 198)	36
Associated nephrolithiasis	29	14

again the frequency of infections of the urinary tract in these patients. Nitrogen retention as indicated by elevated levels of blood urea in more than a third of the patients on the occasion when their polycystic kidneys were first noted, indicates how long they are able to get along without symptoms. The 14% incidence of nephrolithiasis is not as high as some authors have reported (Oppenheimer[24] noted 23.7% in a series of 60 cases), but appears to us to be significant. Hyperparathyroidism secondary to renal failure of long duration may be considered as a possible cause of the calculi, but of the 29 patients who had renal calculi, only 11 had an elevated concentration of urea in the blood. This is 38% or essentially the same incidence found in the group without stones. Stagnation of urine, infection and subsequent formation of calculi, therefore, seem more likely to be the pathogenesis.

The electrocardiograms in these cases showed no changes other than those which might be expected as a result of hypertension of some duration. Left axis deviation was the most common finding and was noted in 71% of 21 cases in which electrocardiograms were made. Changes in T waves were not infrequent, as inverted T waves were present in Lead 1 in 29%, in Lead 2 in 19% and in Lead 3 in 24% of cases. Only 1 instance of right axis deviation was noted.

Necropsy Data. Data derived from 46 necropsies on patients who had polycystic disease of the kidney are given in Tables 7 to 9. Several features may be noted concerning the age at death: 1, the high incidence of children less than 1 year of age, and, 2, the low incidence of patients from 1 to 40 years of age. The first point has been mentioned by Bell who regarded polycystic

TABLE 7. NECROPSY DATA IN 46 CASES CONCERNING AGE AT DEATH, SEX DISTRIBUTION, KIDNEYS INVOLVED AND SIZE AND WEIGHT OF HEART

	Cases	%
Age (years) distribution:		
0-1	9	20
1-9	0	0
10-19	2	4
20-29	1	2
30-39	2	4
40-49	11	24
50-59	11	24
60-69	5	11
70 or more	5	11
Total cases	46	100
Sex distribution: Males	34	74
Females	12	26
Kidneys involved: One	6	13
Both	40	87
Heart, size and weight:		
Hypertrophy of heart noted	24	52
Average weight of these hypertrophied hearts	512 gm.*	

* 2 cases of valvular heart disease excluded.

TABLE 8. CAUSE OF DEATH IN 46 CASES

	Cases	%
Kidney failure with uremia	9*	20
Myocardial infarction	6	13
Cerebral hemorrhage	4†	9
Cardiac failure	3‡	7
Multiple congenital anomalies	3	7
Prematurity	3	7
Generalized peritonitis	6	13
Postoperative, 4		
Postirradiation, 1		
After perforated appendix, 1		
Paralytic ileus (postoperative)	1	
Lobar pneumonia	1	
Bronchopneumonia	2	
Pulmonary edema	1	
Suppurative bronchitis	1	
Lupus erythematosus	1	
Spongioblastoma multiforme	1	
Pulmonary tuberculosis	1	
Hemorrhage from ruptured esophageal varices	1	
Cerebral thrombosis	1	
Basilar meningitis	1	

* One case of chronic glomerulonephritis included.

† Case of one infant with cerebral hemorrhage as a result of birth trauma included.

‡ One case of rheumatic endocarditis included.

TABLE 9. ASSOCIATED CONGENITAL ANOMALIES ENCOUNTERED IN 46 CASES OF POLYCYSTIC DISEASE OF THE KIDNEY AT NECROPSY

Associated congenital anomalies	Cases	%
Polycystic liver	15	33
Polycystic pancreas	4	9
Polycystic spleen	1	2
Cardiac defects	4	9
Defects of nervous system	2	4
Genito-urinary defects (other than polycystic kidney)	6	13
Defects of gastro-intestinal tract	3	7
Defects of the musculoskeletal system	2	4
Total	37	81

disease of the kidney in children as a distinct sub-group. In cases of infantile polycystic kidney disease there is also an unusually high incidence of other congenital anomalies. In 7 of the 9 cases in our series, multiple congenital anomalies were present. It would appear that some major defect in embryonic life affecting most of the organs of the body produces these cases of infantile polycystic kidney disease. The low incidence of death from polycystic disease of the kidney in the age group from 1 to 40 years suggests that some process of aging as well as polycystic disease of the kidney *per se* may be operative in causing these deaths. Hinman's data[12] demonstrating the rapidity with which cystic damage proceeds in a kidney with impaired blood supply, together with the data of Schacht[29], and of Ritter and Baehr[28] on arteriolosclerosis in polycystic kidneys, is suggestive that polycystic kidneys may experience no serious functional difficulty until impaired blood supply weakens the parenchyma and supporting tissue to permit rapid development of the cysts.

The finding of unilateral polycystic disease of the kidney in 13% of the cases studied at necropsy is somewhat unusual, although such cases have been reported. Fevre and Tran Van Hoa[8] found 11 cases (68%) of unilateral disease in 16 cases of polycystic kidneys among children. Bell[2] reported 8 cases of unilateral involvement in a series of 48. Lejars[16] noted 3 cases of unilateral polycystic kidney in his series of 62 cases. Oppenheimer[24] and Lowsley and Curtis[17] reported that in series of 60 and 53 cases, respectively, they found no cases of unilateral polycystic kidney. The impossibility of verifying the diagnosis of polycystic disease affecting only one kidney without necropsy data vitiates much of such data, however.

The causes of death (Table 8) in this series show some interesting features. Slightly under a fifth of the patients died as a result of renal failure. Even if deaths from the effects of hypertension accompanying polycystic kidney disease (cardiac failure, myocardial

infarction, and cerebral hemorrhage) are included, the incidence is still less than 50%. The high postoperative mortality rate (5 deaths may be noted in Table 8) might suggest, as was once felt, that patients with polycystic renal disease are poor surgical risks. The fact that all but one of these deaths occurred before the days of sulfonamides and penicillin indicates that this is no longer true.

The incidence of associated congenital anomalies is shown in Table 9, and reaffirms their reported frequency. Polycystic disease of the liver in particular, is associated with polycystic disease of the kidney. Moschcowitz[20] reported an incidence of 19% and Oppenheimer[24] 28.5% of cystic involvement of the liver in their series of cases of polycystic disease of the kidney. There were no symptoms in our entire clinical group of 207 cases suggestive of polycystic disease of the liver although Waterson and Morgan[36] reported a remarkable instance of jaundice in a patient known to have polycystic disease of the kidney. The jaundice in this case was relieved by evacuation of 284 cc. of fluid from cysts in the liver.

Cardiac hypertrophy was noted in 52.3% of our 46 cases in which necropsy was performed; the average weight of the hearts, exclusive of those with associated valvular heart disease, was 512 gm. The largest weighed 712 gm. This is somewhat at variance with the experience of Bell[2] who reported minimal, if any, cardiac hypertrophy in this disease.

Summary and Conclusions. From our study, we may conclude that the typical patient with congenital polycystic disease of the kidneys will have a family history of renal disease and may expect symptoms to appear during the fourth or fifth decade of life. These symptoms in about two-fifths of the cases will consist of dragging abdominal or lumbar pain accompanied by some abdominal enlargement. A history of recurrent infections of the urinary tract and possibly renal colic may be elicited. On examination one or both kidneys may be palpated as irregular, hard masses. The blood pressure will probably be found to be moderately elevated with minimal to moderate hypertensive changes in the ocular fundi. Laboratory examinations may reveal albuminuria and pyuria of varying degrees. The intravenous pyelogram will show elongated calices with some blunting and irregularity of outline. Such a patient ordinarily will have a life expectancy of approximately 10 years after the onset of symptoms and has a fair chance for a normal life span. A poor prognosis is indicated by increase in the size of the kidneys, increase in severity of symptoms, progression in associated hypertensive vascular disease or advancing impairment of renal function.

Clinical data are presented on 207 proved cases of congenital polycystic disease of the kidney and certain common features emphasized. A more optimistic attitude toward such patients is suggested by an average age at death of almost 50 years. Necropsy data in 46 cases of polycystic disease of the kidney reveal a frequency of unilateral polycystic disease, the common occurrence of associated congenital malformations, and differential features between infantile and adult polycystic disease of the kidney.

REFERENCES

1. **Bagg, H. J.:** Am. J. Anat., **36**, 275, 1925.
2. **Bell, E. T.:** Am. J. Path., **11**, 373, 1935.
3. **Braasch, W. F.:** Surg., Gyn. and Obst., **23**, 697, 1916.

4. **Braasch, W. F.**, and **Schacht, F. W.**: Tr. Am. Assn. Genito-Urin. Surgeons., **25,** 71, 1932.
5. **Brigidi, D. V.**, and **Severi, A.**: Lo Sperimentale., **46,** 1, 1880.
6. **Crawford, R. H.**: Surg., Gyn. and Obst., **36,** 185, 1923.
7. **Dunger, R.**: Beitr. z. path. Anat. u. z. allg. Path., **35,** 445, 1904.
8. **Fevre, M.**, and **Tran Van Hoa:** Presse méd., **53,** 106, 1945.
9. **Forssman, J.**: Beitr. z. path. Anat. u. z. allg. Path., **56,** 500, 1913.
10. **Fuller, C. J.**: Quart. J. Med., **22,** 567, 1929.
11. **Hepler, A. B.**: Surg., Gyn. and Obst., **50,** 668, 1930.
12. **Hinman, F.**, and **Hepler, A. B.**: Arch. Surg., **11,** 578, 1925.
13. **Kampmeier, O. F.**: Surg., Gyn. and Obst., **36,** 208, 1923.
14. **Felix, W.**: The Development of the Uriniferous Tubules From the Metanephrogenic Tissue. In Keibel, Franz and Mall, F. P., vol. 2, p. 846, Manual of Human Embryology, Philadelphia, J. B. Lippincott, 1912.
15. **Kupffer, C.**: Arch. f. mikr. Anat., **1,** 233, 1865.
16. **Lejars, F.**: Du gros rein polykystique de l'adulte, Paris, 1888.
17. **Lowsley, O. S.**, and **Curtis, M. S.**: J. Am. Med. Assn., **127,** 1112, 1945.
18. **McKenna, C. M.**, and **Kampmeier, O. F.**: Tr. Am. Assn. Genito-Urin. Surgeons, **26,** 377, 1933.
19. **Moolten, S. E.**: New York State J. Med., **43,** 727, 1943.
20. **Moschcowitz, E.**: Am. J. Med. Sci., **131,** 674, 1906.
21. **Mutach, A.**: Virch. Arch. f. path. Anat., **142,** 46, 1895.
22. **Nolan, L. E.**: Urol. and Cutan. Rev., **49,** 734, 1945.
23. **Norris, R. F.**, and **Herman, L.**: J. Urol., **46,** 147, 1941.
24. **Oppenheimer, G. D.**: Ann. Surg., **100,** 1136, 1934.
25. **Paus, N.**: Deut. Zeit. f. Chir., **130,** 628, 1914.
26. **Petterson, A.**: Beitr. z. path. Anat. u. z. allg. Path., **33,** 605, 1903.
27. **Ribbert, H.**: Verhandl. d. deut. path. Ges., **2,** 187, 1899.
28. **Ritter, S. A.**, and **Baehr, G.**: J. Urol., **21,** 583, 1929.
29. **Schacht, F. W.**: Arch. Int. Med., **47,** 500, 1931.
30. **Shunkowsky, W. P.**, and **Ssinjoff, W.**: Arch. f. Kinderh., **58, 85,** 1912.
31. **Staemmler, M.**: Beitr. z. path. Anat. u. z. allg. Path., **68,** 22, 1921.
32. **Tarail, R.**: Am. J. Med., **5,** 828, 1948.
33. **Tollens:** Virch. Arch. f. path. Anat., **177,** 477, 1904.
34. **Virchow, R.**: Ibid., **46,** 506, 1869.
35. **Virchow:** Berl. klin. Woch., **29,** 104, 1892.
36. **Waterson, A. P.**, and **Morgan, P. R.**: Brit. Med. J., **1,** 609, 1946.

DIABETIC NEPHROPATHY

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Focal hyalinization in the intercapillary connective tissue of the kidney in diabetes mellitus was described in 1936 by Kimmelstiel and Wilson[10]. They termed this newly recognized lesion intercapillary glomerulosclerosis and related it to a clinical syndrome. Characterizing the latter in addition to diabetes mellitus was proteinuria, widespread edema, hypertension and eventual renal failure.

Murakami[12], shortly after the original publication, also recognized the lesion in a diabetic. In 1938 Anson[2] concluded that the histologic findings of intercapillary glomerulosclerosis may be anticipated if the patient has hypertension and mild diabetes. Derow, Altschule and Schlesinger[4] in 1939 published several case reports of intercapillary glomerulosclerosis and discussed the specificity of the lesion. Widespread vascular degeneration was proposed as a factor in the pathogenesis by Newburger and Peters[13] in 1939. Porter and Walker[15] presented a discussion of the clinical syndrome, as did Siegal and Allen[16]. Herbut[7] found 11 characteristic examples of intercapillary glomerulosclerosis in a large number of autopsies. An excellent study was conducted by Allen[1]. After finding the lesion in 33% of diabetic patients of 40 years or more, he concluded that a new and more reliable criterion was available for the postmortem diagnosis of diabetes mellitus.

The clinical syndrome is not recognized as frequently as is the kidney lesion. This suggests that the glomerular changes do not always result in a nephrotic hypertensive patient. In this regard, Laipply, Eitzen and Dutra[11] tried to correlate the pathologic and clinical components of the syndrome, and found no constant relationship.

At present most authors[1,6,7,11,17,19] agree that the renal lesion is rare in people who do not have diabetes. Siegal and Allen[16] found the lesion in only 1 case during the examination of 200 non-diabetic kidneys. By contrast, Horn and Smetana[8] contend that early examples of focal hyalinization may be found in many non-diabetics who have other kidney pathology. Their conclusion is based upon finding the lesion in nephrosclerosis, generalized arteriosclerosis and glomerulonephritis. Consolidating much of the information available in the literature, Kimmelstiel and Porter[6] recently presented an outstanding review of the diabetic syndrome.

The purpose of this report is to assist in achieving a necessary reorientation. The validity of unconfirmed or partially confirmed presumptions must be determined. Whether or not this lesion is pathognomonic of diabetes has been questioned. A high incidence in the diabetic alone would be of inestimable diagnostic value to the pathologist. Present histologic methods of diagnosis of diabetes are difficult to interpret accurately. Recognition of focal hyalinization, by contrast, presents little difficulty with routine stains.

The clinical aspects of the condition also need clarification. The end stages of the disease have received much

attention in reports stressing the features originally described by Kimmelstiel and Wilson. Uncertainty still exists concerning the clinical recognition of the early pathologic lesions.

Questions of morphology remain. Laipply, Eitzen and Dutra[11] have expanded the criteria set by Kimmelstiel and Wilson[10]. The former describe fibrosis of the glomerulus as an early stage of intercapillary glomerulosclerosis. Their statistics show a rise over all former reports, due to this interpretation. The question, however, is open to further investigation and will be discussed below.

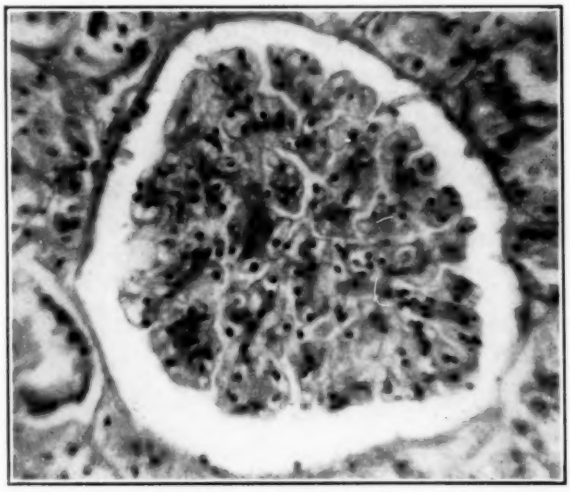

FIG. 1. Diabetic glomerulus demonstrating diffuse involvement of walls of the capillaries. Classified as "minimal" intercapillary glomerulosclerosis.

Material and Method. Fifty consecutive autopsies of diabetic men and women were reviewed. Sections of kidneys were studied with a modified Masson trichrome stain accentuating connective tissue. The lesion when found was reported as minimal, moderate or severe. The criteria for this classification are discussed in our consideration of the morphology.

Grading the severity of diabetes was done arbitrarily on the basis of insulin requirements daily as determined from the clinical histories. Diabetes was considered mild if up to 15 units of insulin were required; moderate if 16 to 40 units; and severe if 40 or more units were required daily.

The blood pressure reading selected was taken to represent the patient in his most basal condition. Instances existed where complications obscured the true readings. Therefore, hypertension in most cases was confirmed by the size of the heart at necropsy. Separation of the normal from the hypertensive group was accomplished by using systolic pressure of 150 mm. and diastolic pressure of 90 mm. as the point of division.

The clinical charts were examined for data as to sex, duration of the disease, proteinuria, azotemia, and the nephrotic syndrome.

To correlate the lesion with the duration of diabetes the patients were divided into groups of 5 year intervals up to 15 years' duration. All those above the latter figure were grouped together. The information in many cases was questionable; these were called "unknown duration" and eliminated from consideration. For further elucidation the average duration of diabetes was analyzed and graphed.

Patients were regarded as having had moderate nitrogen retention or azotemia when the blood urea nitrogen was in the range of 40 to 60 mg. per 100 cc. Arbitrarily all above the latter figure were called uremic. In many cases renal and pre-renal azotemia due to heart failure could not be differentiated.

The nephrotic syndrome includes patients with plasma proteins below 5.5 gm. per 100 cc., proteinuria of long standing, generalized edema and hypercholesterolemia.

When the cholesterol was not reported but other criteria were typical we did not hesitate to include the case in our group.

In demonstrating the relationship of intercapillary glomerulosclerosis and arteriosclerosis, we used gangrene as indicative of advanced peripheral vascular disease. In all these cases amputation had been performed or a gangrenous lesion was found at autopsy. While many extrinsic factors exist in the etiology of gangrene in diabetes, advancing arterial and arteriolar sclerosis is the basic defect. In an attempt to relate the two pathologic processes others have compared the degree of renal vessel sclerosis with the stage of development of intercapillary glomerulosclerosis. We have approached the problem (comparing peripheral vascular pathology with advancing diabetic nephropathy) to reach a conclusion fortified by additional facts.

The controls used in the estimation of the histologic lesion were 50 non-diabetics of a corresponding age group with kidney involvement such as benign nephrosclerosis, chronic glomerulonephritis, and chronic pyelonephritis.

MORPHOLOGY OF THE LESION. The typical lesion consists of spherical, dense hyalinized material between the glomerular tufts which appear homogeneous under low power. Under higher magnification one can see circumferential laminated structures containing a few very small vacuoles. This hyaline does not react positively to stains that show amyloid. It is acidophilic with hematoxylin and eosin and stains green with modified Masson trichrome stain. Around the spherical lesion there are flattened cells in concentric layers. The center of the lesion usually contains no cells, but on occasion the remnants of a pyknotic nucleus may be found. The size varies from that of a small number of cells to involvement of an entire glomerulus. In the late stages the latter is often shrunken. Thickening of the afferent arteriole is often seen.

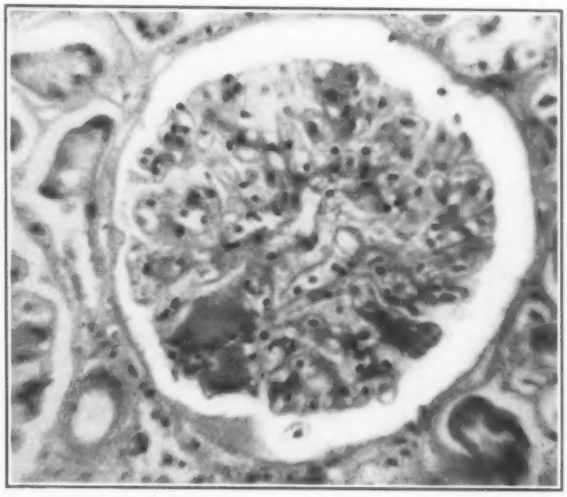

FIG. 2. A typical spherical hyaline body in the glomerulus of a diabetic. Classified as "moderate" intercapillary glomerulosclerosis.

All degrees of involvement may be found in one glomerulus or it is possible to find only one lesion in several sections of the kidney. In sections showing the lesions many of the glomeruli show evidence of fibrosis. The lesion may not be apparent in the typical spherical form, but focal or diffuse fibrosis of the connective tissue of the glomerulus leads to more intense study and eventually the hyaline oval

mass will be found. For this reason we recognize glomerular fibrosis as a lesser involvement which may progress to the spherical lesion. Others[11] have reported this stage of intercapillary glomerulosclerosis in 24% of the diabetic patients with the lesion. Our figure is confirmatory, placing the incidence slightly higher. The validity of the association of lesions can often be demonstrated by searching through many sections of the same kidney. In addition to the glomerular fibrosis, an occasional hyalinized glomerular tuft can be seen. It is possible that benign nephrosclerosis, chronic pyelonephritis, or chronic glomerulonephritis will simulate this closely. These lesions have variations in fibrosis from one glomerulus to the next in addition to other changes which do not occur in intercapillary glomerulosclerosis. The diffuse lesion, however, is not always readily identified as specific for diabetes.

Glomerular fibrosis described in disseminated lupus erythematosus should not be confusing. Other findings in this disease include focal necrosis in many of the glomeruli which is missing in the diabetic kidney. Finding the characteristic "wire loop" of lupus erythematosus makes separation definite.

In our study fibrosis of the glomerulus was classified as the minimal lesion of intercapillary glomerulosclerosis. Glomeruli containing occasional spherical hyalinized lesions were listed as moderately involved. The advanced lesion was considered present when hyalinization existed in all glomeruli.

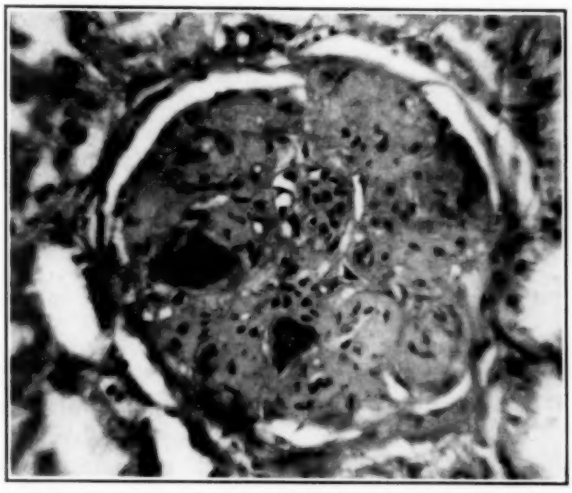

FIG. 3. A classical lesion of the advanced clinical syndrome in diabetes. There is complete involvement of the glomerulus by the disease process. Classified as "advanced" intercapillary glomerulosclerosis.

Whether or not diabetic glomerulosclerosis is "intercapillary" has raised conjecture. This descriptive term was given by Kimmelstiel and Wilson because they believed the lesion developed from hyalinization of the connective tissues between the capillaries. Allen[1] questioned this hypothesis. After studying the nature of hyalinization and observing staining qualities, he concluded that the hyaline is deposited in the wall of the capillary loop, and

a more accurate description would be "intramural" glomerulosclerosis. Serial sections of the lesion have affirmed this conclusion. The three dimensional description of the hyalinization would present the spherical lesion as a focal mass of hyalinization through which the capillary courses. Hyalinization and thickening extend from the capillary system in the glomerulus to the afferent arteriole where the intramural hyalinization is easily recognized[3]. Unfortunately the term "intercapillary" seems too deeply entrenched in the literature to be replaced. With misgivings, but for uniformity, we shall retain the original term.

INCIDENCE OF INTERCAPILLARY GLOMERULOSCLEROSIS. In our series, glomerular disease was discovered in 82% of the diabetics (Table 1). Previous studies place the incidence between 20.5 and 63.5%. Authors and their figures are given (Table 2). Increasing recognition of the stage of fibrosis by many authors explains the increase in incidence in recent studies.

By including in the controls non-diabetic nephrosclerotics and glomerulonephritics, we were able to discover whether the lesion of spherical hyaline change was present in other pathologic conditions, as has been claimed[8]. The control group studied affirms previous conclusions that moderate or advanced intercapillary glomerulosclerosis is rare in the absence of diabetes[1,6,7,11,17,19]. Our figure of 2% incidence of moderate or advanced lesions in non-diabetics is based on finding the typical lesion in a 63 year old female who died on admission. Since blood sugar and urinary sugar determinations were not made, the possibility of diabetes cannot be excluded. This case may be similar to other reported non-diabetics who present evidence of the hyaline change of intercapillary glomerulosclerosis. The minimal lesion was indistinguishable from many lesions found in non-diabetics. Hence no accurate estimate of its specificity can be made.

Latent diabetes may account for the discovery of intercapillary glomerulosclerosis in the absence of glycosuria. The glucose tolerance test should be used to evaluate suspicious cases. This test becomes altered from normal to one approaching or resembling the diabetic as aging progresses. Goodof[6] found intercapillary glomerulosclerosis in 30% of non-diabetic patients over the age of 70 years, but stated that unfortunately the glucose tolerance test was not available for the material used in his study. In a similar number of non-diabetics between the ages of 5 and 25 years, evidence of intercapillary glomerulosclerosis could not be found.

Table 1 presents an analysis of the degree of involvement by a breakdown of the positive cases. The advanced lesion existed in 8% of the diabetics. Moderate involvement was present in 40%. Minimal changes accounted for

TABLE 1. INCIDENCE OF INTERCAPILLARY GLOMERULOSCLEROSIS IN DIABETIC AND NON-DIABETIC NEPHROPATHY.

	Total Cases	Present	Absent	Minimal	Moderate	Advanced
Diabetic	50	41 (82%)	9 (18%)	17 (34%)	20 (40%)	4 (8%)
Non-Diabetic	50	8 (16%)	42 (84%)	7 (14%)	1 (2%)	

TABLE 2. REPORTED INCIDENCES OF INTERCAPILLARY GLOMERULOSCLEROSIS IN DIABETICS.

Author	Year	Percentage
Siegal and Allen	1941	33.3%
Allen	1941	33. %
Horn and Smetana	1942	22.9%
Bell	1942	20.5%
Spuhler	1943	50. %
Laipply, Eitzen and Dutra	1944	63.5%
Goodof	1945	44. %

34%. Thus the advanced and moderate degree of involvement constituted 48% of the cases studied. This group of moderate or severe involvement is regarded as specific for diabetes. By including the group classified as minimal, the incidence of the lesion rises to 82% in our series, but concurrently the specificity falls as predicted by Kimmelstiel and Porter[9]. The diffuse or minimal degree of involvement cannot be accurately distinguished from other glomerular changes, although we presume these changes are involved in the pathogenesis of the hyaline spherical lesions.

There are explanations for the divergence of reported incidence. It has been estimated that there are from 1 to 4 million glomeruli in each kidney. An average histologic preparation contains a thin section of from 25 to 100 glomeruli. Therefore, failure to demonstrate the lesion after a study of a single section does not exclude the possibility of intercapillary glomerulosclerosis existing in the millions of unexamined glomeruli. It follows that examination of each glomerulus theoretically would provide the most accurate appraisal of the incidence of intercapillary glomerulosclerosis.

TABLE 3. DEGREE OF INTERCAPILLARY GLOMERULOSCLEROSIS IN RELATION TO THE SEVERITY OF THE DIABETES.

Degree of Diabetes	Degree of Sclerosis: Minimal	Moderate	Advanced	Total	%
Mild	8	7	4	19	46.3
Moderate	7	9	0	16	39.0
Severe	2	4	0	6	14.7

Why certain diabetics have the renal lesion and others do not, has not been explained. Discovery of involvement of 48% hyaline lesions and 34% diffuse lesions in our diabetic series arouses conjecture. Intercapillary glomerulosclerosis possibly could be a constant accompaniment of diabetes mellitus. If we performed the ideal examination of all the glomeruli referred to above, the

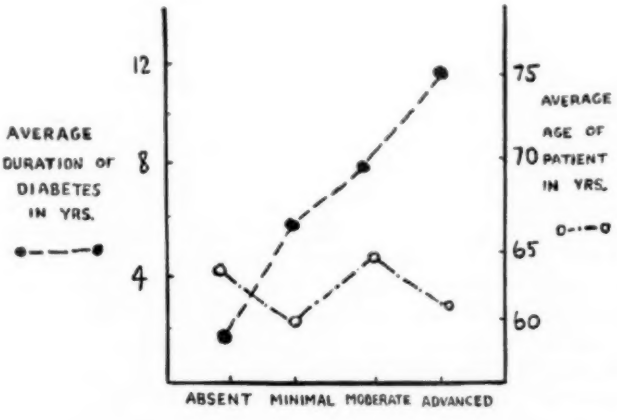

Chart 1. Relation to Duration of Diabetes and Age of Patient to Degree of Intercapillary Glomerulosclerosis.

lesion could conceivably be discovered in the remaining 18%. The pertinent problem of incidence has resolved itself to explanation of why the lesion is absent, rather than its presence.

There does not seem to be a marked predominance of the lesion in either sex. Females were 48% of all the diabetics examined while they comprised 54% of those presenting lesions of intercapillary glomerulosclerosis. Newburger and Peters[13] found 5 of 7 cases to be females. Herbut[7] reported 6 females and 3 males in his study of 9 cases. Goodof[6] believes the disease is more prevalent in women and states

more severe kidney complications than the person whose diabetes is controlled by diet alone? Is there a cause and effect relationship between the duration of diabetes and the advanced lesions, as there is in coronary sclerosis[18]? What role does insulin play in the pathogenesis of intercapillary glomerulosclerosis?

Table 3 demonstrates that almost half the kidneys with the hyaline lesion were from persons with mild diabetes. This group included the 4 kidneys with the advanced lesions. Severe diabetes, which was present in 24% of the entire group, accounted for

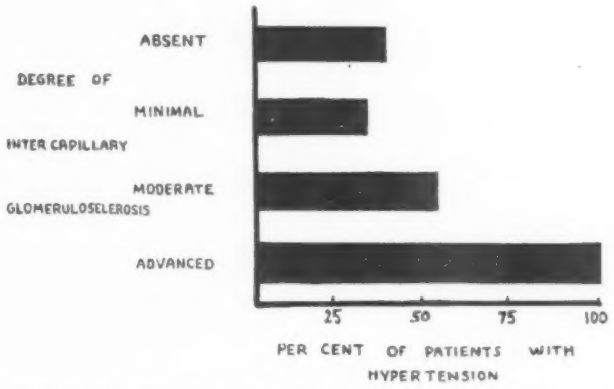

Chart 2. Incidence of Hypertension in the Different Degrees of Glomerulosclerosis.

a ratio of 7 out of 10. Other workers have reported a predominance in women over men varying from 30 to 60%. In our series 4 out of 5 diabetics were found to have the lesion. Thus the incidence of intercapillary glomerulosclerosis is closely related to the incidence of diabetes. The predominance of diabetes in the female can be expected to reflect in studies of sex incidence in intercapillary glomerulosclerosis. Given an equal number of male diabetics and female diabetics, we presume no predominance of the lesion will exist in either sex.

Relation to Diabetes Mellitus. Does the severe diabetic suffer from

only 14.7% of the cases of intercapillary glomerulosclerosis. These facts suggest that severe diabetics do not develop the lesions more frequently nor do they tend to have the advanced type of intercapillary glomerulosclerosis.

Comparison of the incidence of intercapillary glomerulosclerosis with the known duration of diabetes mellitus reveals that in the group having diabetes over 15 years all had the renal complication. Similarly, Goodof[6] found a constant increase in the incidence of intercapillary glomerulosclerosis with increase in duration of diabetes above 6 years. However, Laipply, Eitzen and Dutra[11] did not find correlation

between either the presence or degree of involvement of the glomerular lesion with the known duration of diabetes mellitus.

In our series the average known duration of diabetes in the minimal lesion was 6 years (Chart 1), while those with advanced degree of involvement was 12 years. There is an ascending line when average duration of diabetes is plotted against degree of involvement, giving the impression that we are dealing with a steadily progressive disease. As demonstrated, the age factor is easily excluded from the pathogenesis. The chances for a person to develop kidney complications increase each year he lives with his diabetes, but is apparently unrelated to his age. The progression of the lesion is unrelenting and appears to be unaffected by therapy.

Insulin has been mentioned as a possible cause of the lesion[17]. The severe diabetic in our series was also the one who received the greatest amount of insulin. Since the factor of severity of diabetes does not affect progression of intercapillary glomerulosclerosis, insulin cannot be regarded as significant in the pathogenesis of the lesion.

Hypertension. It has been estimated that 50% of all diabetics have hypertension[18]. In our study, 52% of the diabetics were hypertensive. The percentage was similar to this in those with no discernible intercapillary glomerulosclerosis, those with minimal and those with moderate involvement. In the group with advanced renal changes, however, all suffered from hypertension (Chart 2).

Goodof[6] discovered hypertension in 50% of 88 patients with intercapillary glomerulosclerosis. In most of the reports occurring in the literature shortly after the original publication, the presence of hypertension in the clinical syndrome was stressed. But these reports usually concerned severe lesions corresponding to our group of advanced intercapillary glomerulosclerosis. Later workers included many cases on the basis of only moderate kidney changes.

Laipply and his associates[11] found no correlation between hypertension and the incidence or degree of involvement of intercapillary glomerulosclerosis. We agree with this conclusion on the basis of our findings in those kidneys minimally or moderately involved. Normal blood pressure is wholly consistent with the diagnosis of intercapillary glomerulosclerosis early in the course of involvement. However, the small group of diabetics who have advanced involvement are usually hypertensive.

To explain all hypertension in diabetes by the presence of the spherical hyalinized glomerular lesion would obviously be fallacious. Arteriolar sclerosis plays a significant part, as it does in non-diabetics, and presumably can adequately explain the hypertension in those cases which at necropsy show only minimal changes of intercapillary glomerulosclerosis.

Proteinuria and the Nephrotic Syndrome. Correlation of proteinuria and edema with intercapillary glomerulosclerosis is difficult. Occasionally instances are found where there is generalized edema but less proteinuria than in cases with minimal swelling of the ankles[7]. Newburger and Peters[13] found that early in the course of the disease proteinuria was present in a varying degree but that terminally it was usually very profuse. Others have had similar experience. Mild lesions have often shown little or no proteinuria[6], while series of patients with advanced lesions have been almost uniform in the excretion of large amounts of protein in the urine[11].

Accurate statistical appraisal is difficult because there may be many com-

plicating factors obscuring true proteinuria on a basis of intercapillary glomerulosclerosis. Pre-renal causes for proteinuria in diabetes are common. Many in our group of cases were in congestive failure. Some had peripheral gangrene and a few were in coma due to ketosis. Arterial and arteriolar sclerosis may adequately explain a portion of the proteinuria found. Nevertheless, certain trends are apparent. In the groups of mild and moderate lesions many had no proteinuria while a few had severe proteinuria. There does not seem to be correlation between the degree of the lesion and the amount of protein found in the urine, if the advanced lesions are deleted from consideration. The markedly advanced cases all had 3 to 4+ proteinuria. It seemed to be a fairly constant accompaniment of this type of lesion. While lack of proteinuria would be against the diagnosis of advanced intercapillary glomerulosclerosis its presence does not necessarily indicate severe involvement of the glomerulus.

The nephrotic syndrome, when it occurs, has characteristic features including proteinuria, low blood proteins, elevated blood cholesterol and universal edema. The nephrotic syndrome was present in 12.2% of our cases with diabetic kidney damage. Examination of the type of renal lesion usually associated with the nephrotic syndrome revealed that in 3 patients the spherical hyaline changes were severe. In the other 2 the lesion was classified as moderate. The syndrome was not observed in the absence of intercapillary glomerulosclerosis. Since the syndrome was not present in conjunction with minimally involved kidneys, it is a sign of late intercapillary glomerulosclerosis. If the diagnosis of kidney change were made only when the classical picture of anasarca appeared, more than 4 out of 5 cases of the disease would be missed. The syndrome is of ominous prognostic significance. It indicates that the kidneys are hopelessly involved.

Chart 3. Incidence of Renal Failure in Relation to Degree of Intercapillary Glomerulosclerosis.

While morphologic study is not a complete method of estimating functional integrity of the kidney or any other organ, nevertheless certain conclusions seem justifiable. From the nature of the lesion it may be expected that the minimal stage presumably should not affect kidney function, while moderate glomerular involvement in the absence of other pathologic findings should leave the kidney with enough functional reserve to clear waste products efficiently. The advanced lesion, however, affecting

almost every glomerulus with marked hyalinization, sooner or later will lead to nitrogen retention. Severe uremia may possibly be precipitated with the addition of pre-renal factors such as cardiac failure or acidosis. Examination of Chart 3 confirms the ideas gained from the morphologic studies. As the lesion advanced in severity, the percentage of patients with moderate nitrogen retention and uremia showed progression until all the severe cases had either moderate kidney failure or uremia.

Proteinuria, edema resulting from hypoproteinemia and nitrogen retention are manifestations to be taken as evidence of advancing renal failure and not as significant signs of any particular disease of the kidneys.

Relationship to the Arteriosclerotic Process. Arterial and arteriolar sclerosis is known to be related to diabetes mellitus. It has been demonstrated that progression of arteriosclerosis is accelerated by this disease. Coronary artery sclerosis is encountered more frequently in the diabetic than in the non-diabetic, and when coronary sclerosis is present it has a poor prognosis in the presence of diabetes[18]. Because of the possibility of renal vascular sclerosis being a causative factor, most papers on the subject have mentioned the high incidence of advanced cardiovascular sclerosis with intercapillary glomerulosclerosis. Newburger and Peters[13] believe the pathogenesis of intercapillary glomerulosclerosis is directly related to severe arterial and arteriolar degeneration. By contrast Siegal and Allen[16] excluded the possibility that the lesion is secondary to marked nephrosclerosis because of its presence in cases of diabetes without renal vascular complications. According to Herbut[7], benign nephrosclerosis is an accompanying lesion in most cases, but he has seen examples especially in younger people where intercapillary glomerulosclerosis is the only renal lesion. Since it is recognized that patients with mild diabetes do have accelerated vascular changes and that frequently the vascular changes are more pronounced in one area of the vascular tree than in another, Porter and Walker[15] suggested that capillary changes may represent another instance of predilected degenerative processes. Laipply, Eitzen and Dutra[11] recognized that those kidneys with the greatest degree of intercapillary glomerulosclerosis had the most pronounced vascular changes, but believed that the incidence would have to be expected, since intercapillary glomerulosclerosis is present in the same age group as persons with advanced sclerosis. They agree that it is contributory, but do not believe that it is the sole factor.

In our group of 50 non-diabetic kidneys, most of which were examples of nephrosclerosis, only 1 case with a spherical hyaline lesion was found. Causal relationship implicating vascular sclerosis is not suggested by this finding.

Arteriosclerosis obliterans was found in 50 of 100 diabetics selected at random by Pearl and Kandel[14]. This advanced arteriosclerotic degenerative process has been estimated to be 11 times as frequent in diabetics as in non-diabetics of comparable age groups[5]. Progression of arteriosclerosis obliterans ultimately results in gangrene. The high incidence of this complication in diabetics is well known. We compared far advanced peripheral arteriosclerosis, as roughly measured by the incidence of gangrene, with the degree of involvement of the kidney by intercapillary glomerulosclerosis. In the diabetic group which did not have any evidence of intercapillary glomerulosclerosis the incidence of gangrene was 22%. Of those with the diagnosis of intercapillary glomerulosclerosis, 24% had gangrene of an extremity, while of those having

the most advanced intercapillary glomerulosclerosis 25% had severe arteriosclerosis obliterans as measured by peripheral gangrene. These figures arouse speculation. Were vascular disease a prominent etiologic factor in intercapillary glomerulosclerosis, we would expect a higher incidence of gangrene in those with far advanced kidney disease. While correlation of pathologic processes by this method may be open to question, nevertheless the figures are of enough significance to be convincing. The basic importance of arterial and arteriolar sclerosis in causing intercapillary glomerulosclerosis seems most unlikely.

Summary. The literature reveals differences of opinions and theories concerning specific renal change in diabetes. The objective of this paper has been to reduce these opinions and theories to a concise presentation, and to correlate this with our own findings.

Recent reports have considered ever higher estimates of the incidence of intercapillary glomerulosclerosis in diabetics. The concept that intercapillary glomerulosclerosis is a frequent accompaniment of diabetes mellitus of long standing is given support. In one decade this is a marked alteration in the knowledge of the pathology of the diabetic kidney.

Hypertension, proteinuria, the nephrotic syndrome and renal failure are shown to be unrelated to the involvement of the kidney, except in those few cases in which the lesion is far advanced. In the latter instance the components are usually found to make the clinical diagnosis of intercapillary glomerulosclerosis obvious. Before this stage is reached, we can only speculate on the amount of focal hyaline change that is taking place. It is reasonable to assume, however, that progression of the renal lesion will take place irrespective of therapy. With increase in the average length of life expectancy for well-controlled diabetics, we must be more aware of the pathogenesis and pathology of this complication of the metabolic disease.

Arteriosclerosis presumably is a separate problem in diabetes. While etiologic factors may be similar to those of intercapillary glomerulosclerosis, the pathogenesis of the two conditions at present does not appear to be closely related.

REFERENCES

1. **Allen, A. C.**: Arch. Path., **32**, 33, 1941.
2. **Anson, L. J.**: South. Med. J., **31**, 1272, 1938.
3. **Bell, E. T.**: Am. J. Path., **18**, 744, 1942.
4. **Derow, H. A., Altschule, M. D.,** and **Schlesinger, M. J.**: New England J. Med., **221**, 1012, 1939.
5. **Dry, T. J.,** and **Hines, E. A.**: Ann. Int. Med., **14**, 1893, 1941.
6. **Goodof, I.**: Ann. Int. Med., **22**, 373, 1945.
7. **Herbut, P. A.**: Arch. Path., **31**, 501, 1941.
8. **Horn, R. C., Jr.,** and **Smetana, H.**: Am. J. Path., **18**, 93, 1942.
9. **Kimmelstiel, P.,** and **Porter, W. B.**: (a) New England J. Med., **25**, 876, 1948; (b) 26, 908, 1948.
10. **Kimmelstiel, P.,** and **Wilson, C.**: Am. J. Path., **12**, 83, 1936.
11. **Laipply, T. C., Eitzen, O.,** and **Dutra, F. R.**: Arch. Int. Med., **74**, 354, 1944.
12. **Murakami, R.**: Tr. Soc. path. jap., **26**, 657, 1936.
13. **Newburger, R. A.,** and **Peters, J. P.**: Arch. Int. Med., **64**, 1252, 1939.
14. **Pearl, F. L.,** and **Kandel, A.**: Arch. Surg., **39**, 86, 1939.
15. **Porter, W. B.,** and **Walker, H.**: J. Am. Med. Assn., **116**, 459, 1941.
16. **Siegal, S.,** and **Allen, A. C.**: Am. J. Med. Sci., **201**, 516, 1941.
17. **Spuhler, O.**: Schweiz. med. Woch., **73**, 1430, 1943.
18. **Stearns, S., Schlesinger, M. J.,** and **Rudy, A.**: Arch. Int. Med. **4**, 463, 1947.
19. **Zollinger, H. V.**: Schweiz. med. Woch., **73**, 1432, 1943.

ALBUMINURIA IN SERVICE RECRUITS: A LABORATORY STUDY OF 193 CASES REFERRED FROM ROUTINE MEDICAL EXAMINATION

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The occurrence of albuminuria in persons otherwise free from evidence of disease has presented a problem ever since its first discovery. Many observers have attempted to classify such cases and some of their publications, briefly reviewed here, show how diverse the significance of symptomless albuminuria may be. The present report summarises the results of our own observations, which have been made throughout a period of 7 years, 1942-48, and are derived from laboratory investigations of 193 young adults who, at their routine medical examination for recruitment into the Services, had all shown symptomless albuminuria. The subjects were referred to us for an independent opinion as to the probable significance of the albuminuria.

Historical Perspective. In 1694 Dekkers discovered albumin in urine, making use of what is now the boiling test, but it was not until 1827 that Bright associated albuminuria with nephritis (see Dukes[10]). According to Young *et al.*[32] who have surveyed the literature, Becquerel[5] (1841) was the first to record albuminuria in a young adult, unaccompanied by evidence of renal disease; Vogel[30] (1864) noted a similar instance. "Remittent" albuminuria was first studied by Moxon[21] in 1878 and in the same year von Leube[17] published his finding that 4% of apparently healthy soldiers had albumin in their urine. Pavy[22] described a so-called "cyclic" albuminuria, while Stirling[27] (1887) first proved the existence of a definite condition to which he accorded the term "postural albuminuria"; Teissier[28] (1899) called this same condition "albuminurie orthostatique". The benign nature of this type of proteinuria was doubted by Senator[26] (1904) who concluded that it indicated some degree of renal abnormality. In 1905 Dukes[9] recorded the presence of albumin in the urine of 16% of schoolboys and ascribed their proteinuria to instability of the cardiovascular system; when the subjects were later tested as adults they were all albumin-free. Jehle[13] concluded from a study of 300 children that their albuminuria was due to hyperemia of the kidney caused by lordosis of the lumbar spine. The production of albuminuria by severe physical effort was noted by Collier[7] when he tested the urine of each member of the Oxford boat crew in 1906, immediately after the race.

With regard to incidence, so far as young adults are concerned, McLeod and Ameuille[20], in examining 2,000 soldiers, noted albuminuria in 2.9%, casts in the micro-deposit in 0.86% and red cells in 0.66%. MacLean[19] found albuminuria in 5.8% of 60,000 men, the incidence being the same in

a group of 10,000 before military training and in a group of 50,000 after training. The albuminuria was slight in 3%, considerable in 2.8%; while in only 1.1% was there an abnormal urinary micro-deposit. Theobald[29], examining 5,000 Post-Office girls, noted albuminuria in 6.7%.

Lee[16], Fox[11] and Bashford[3] have all concluded from long-term observations that adolescent albuminuria is a condition which does not develop into renal disease, and the benign nature of orthostatic albuminuria has been substantiated by the biochemical studies of Post and Thomas[23] and of Schultz and Swanson[25]. However, caution was expressed by Gulland[12] who believed that slight degrees of nephritis might often occur wherein renal efficiency tests alone failed to demonstrate defective kidneys. Moreover, Russell[24] pointed out that some instances of orthostatic albuminuria might represent a stage in resolving nephritis, especially of scarlatinal or diphtheritic origin, though Diehl and McKinlay[8] could find no statistical significance in the incidence of precursory diseases.

In 1941, Lyall[18] published results of his study of 110 men who showed albuminuria on more than one occasion when examined for recruitment to the Services. Other recent contributions include those by Young *et al.*[32] on orthostatic albuminuria; Ahronheim[1] and an annotation[2] on emotional albuminuria; and a leading article in the Lancet[15] on albuminuria in the young. Wolman[31] has also surveyed the whole problem and recorded valuable observations on 420 apparently healthy men (out of 22,000 entering the U. S. Maritime Service) who had proteinuria, mostly intermittent in type but persistent in 7 cases, significant of mild unsuspected nephritis in 8 cases and of urologic disease in 3 cases. Wolman also deduced that random urinalysis of single specimens will usually reveal cases of nephritis though it will often fail to demonstrate cases of urologic or benign intermittent proteinuria. In studying such cases, the concentration of protein in random specimens of urine was not found to be diagnostically helpful. Our own observations were begun at the end of 1941 and continued to the end of 1948.

Scheme of the Investigation. The 193 subjects studied comprised 187 males and 6 females, all civilians, and referred from primary routine medical examination for recruitment into the Services. Their mean age was 19.7 years (standard deviation 4.8) and the range 14 to 43 years. Most of the subjects were age 17 to 24, though 14 had ages from 27 to 43 years and 2 cadets were aged 14. They had all shown albuminuria on 2 or more occasions at routine medical examination but none had clinical evidence of renal disease.

On arrival at the laboratory, each subject provided an initial (ambulant) urine, a first-hour specimen after sitting and a second-hour specimen after lying down. This procedure was found to be an adequate (but not rigorous) test for the existence of postural albuminuria. Although many of the patients brought with them a sample of urine passed on waking in the morning and these also were examined, especially for specific gravity and pigment concentration, no exclusive reliance was placed on the results, because there was no guarantee as to their origin or ownership. The initial (ambulant) urine was examined for the presence of red or white corpuscles or casts in the micro-deposit and all samples were tested for the presence of protein by the boiling test or with salicylsulphonic acid. Quantitative determinations of protein were carried out in selected cases. Blood urea concentration was determined by the method of King *et al.*[14] and urea clearance value by the procedure as described by Beaumont and Dodds[4].

Results. The distribution of cases is shown in Table 1 where they are divided into 5 groups according to the type of albuminuria and the character of the micro-deposit. Of the total persons investigated, 53 showed no albuminuria when tested at the laboratory and their urine never contained red or white corpuscles or casts. It was noted that several individuals gave

a history of "colds" or sore throats at the time of their medical examination and altogether this group ("albuminuria-absent") is regarded as affording examples of transient, intermittent or emotional albuminuria, devoid of pathological significance, but forming a valuable (negative) control with which to compare the positive groups. These 4 groups correspond closely to Lyall's[18], except that in our series all the nephritis cases are together, whereas Lyall divided his into subacute and chronic or subchronic.

noted in this group was 600 mg. per 100 cc.

The group where albuminuria is described as "due to nephritis" comprises 19 men. Of these, 8 had erythrocytes in the urinary deposit, 3 had granular or red cell casts, and 8 had both erythrocytes and casts. The albuminuria was constant in 9 cases, somewhat diminished by recumbency in 7 cases and completely abolished by recumbency in 3 cases. The highest urine protein concentration found was 400 mg. per 100 cc., a value notably

TABLE 1. DISTRIBUTION OF 193 CASES OF ALBUMINURIA IN 5 GROUPS

Type of albuminuria	Present Series No.	Present Series %	Present Series No.	Present Series %	Lyall's Series No.	Lyall's Series %
Postural	65	34	65	46	31	28
Persistent	41	21	41	29	22	20
Due to nephritis	19	10	19	14	45	41
Due to infection	15	8	15	11	12	11
Absent	53	27				
TOTAL	193	100	140	100	110	100

TABLE 2. SUMMARY OF BIOCHEMICAL FINDINGS IN 5 GROUPS OF 193 CASES OF ALBUMINURIA.

Type of Albuminuria	No. of Cases	Blood Urea mg. per 100 cc. Mean	Blood Urea mg. per 100 cc. S.D.	Abnormal Blood Urea Values	Urea Clearance % of normal Mean	Urea Clearance % of normal S.D.	Abnormal Urea Clearance Values
Absent	53	28	6	44[1]	114	34	
Postural	65	28	7	44[2]	123	37	35[2]
Persistent	41	28	6		114	24	
Due to nephritis	19	35	9	60[3], 43[4], 46[5]	95	45	29[3], 39[4]
Due to infection	15	31	8	47[6], 42[7]	99	41	31[6]

In the group "postural albuminuria", the characteristic features were an insignificant micro-deposit and an initial albuminuria which became completely abolished by recumbent posture. The highest urine protein concentration recorded was 1,100 mg. per 100 cc.

In the group "persistent albuminuria" there was likewise an insignificant micro-deposit throughout. Excretion of protein was continuous, though it was often lessened by inactivity and further diminished by recumbent posture. The highest urine protein concentration

less than that found within the groups where albuminuria was considered to be devoid of pathological significance. All the cases in the nephritis group are thus seen to have been characterised by the nature of the micro-deposit, while in most of them there was also a persistent albuminuria as well. In 3 instances within this group, confirmatory evidence of renal functional impairment was also obtained by biochemical tests.

In the last group, "albuminuria due to infection", 12 subjects out of 15

showed a persisting albuminuria while 3 had protein-free urine after recumbency. The highest protein concentration noted was 80 mg. per 100 cc. urine. In the micro-deposit, 9 had red corpuscles, none had casts, but all showed a significant number of pus cells. Cultures yielded *B. coli* from 4, *Proteus vulgaris* from 1, while microscopic search revealed *M. tuberculosis* from 1 and *N. gonorrhoeae* from 1. The remaining 8 urines yielded inconclusive results from bacteriological studies but were regarded as containing indirect evidence of infection.

Table 2 summarizes the biochemical data; blood urea and urea clearance figures are recorded as mean values with standard deviations for each group. Using the critical levels defined by Mean ± 2.S.D., afforded by the control group "albuminuria absent", a number of abnormally high blood urea values (over 40 mg. per 100 cc.) and low urea clearance values (under 46%) are noted for special consideration. These abnormal values characterised 7 subjects with high blood urea concentrations; of these, 4 had also abnormally low urea clearance values. More complete details of these 7 cases are recorded in Table 3.

Discussion. In Table 1 the numerical distribution of cases in Lyall's[18] series is noted alongside ours for comparison. The greatest differences are seen in the group "postural albuminuria" where our proportion is higher and in "albuminuria due to nephritis" where our proportion is lower. Since Lyall's tests for postural albuminuria were more rigorous than ours, in that his tests for absence of protein were done on overnight samples whereas ours were made with only 1 hour recumbent specimens, it would seem that the different proportions of "postural albuminurias" arise merely from chance in the samples of population studied. Any difference arising from

TABLE 3. DETAILS OF 7 CASES CHARACTERIZED BY ABNORMAL BIOCHEMICAL FINDINGS

Case No.	Age	Albuminuria A.	Albuminuria S.	Albuminuria L.	Micro-Deposit RBC	Micro-Deposit WBC	Casts	Blood Urea mg. per 100 cc	Urea † Clearance % of normal	Type of Case
1.	18	—	—	—	—	—	—	44	(76)	Blood urea not significant.
2.	17	+	—	—	—	—	—	44	35	6/12 post-nephrectomy.
3.	21	+	+	+	+	—	++	60	29	Nephritis.
4.	17	+	+	+	+	—	—	43	39	Nephritis.
5.	18	+	—	—	+	—	+	46	(71)	Nephritis.
6.	18	+	+	+	—	+	—	47	31	Pyuria.
7.	18	+	+	+	+	+	—	42	(82)	Pyelonephritis.

A = Ambulant. S = Sitting. L = Lying down.

† Urea clearance values in brackets are not significantly diminished.

the procedure adopted would have tended towards the finding of a smaller proportion of postural type in our series instead of the larger proportion which was, in fact, found.

It is noteworthy that our group of nephritis cases did not include any individuals with clinical evidence of nephritis, whereas that of Lyall did. If those with "clinical" nephritis are segregated, a remaining 21% of Lyall's patients appear as having asymptomatic albuminuria due to nephritis. This percentage is now comparable with our figure of 14%.

Finally from Table 1 it is seen that the proportion of individuals whose albuminuria was attributed to infection was the same in Lyall's series and in our own.

The results of the biochemical investigations, as summarized in Tables 2 and 3, show abnormally high blood urea concentrations in 7 cases, accompanied in 4 instances by abnormally low urea clearance values. Regarding Table 3, it may be noted that Case 1 showed a slightly raised blood urea which was ultimately discarded as clinically insignificant, while Case 2, a postural albuminuria, had abnormal values ascribed to previous nephrectomy. Of 3 cases of nephritis with raised blood urea, 2 showed also a diminished urea clearance; while of the 2 cases of infection with raised blood urea, 1 showed a diminished urea clearance.

The urea clearance test is generally regarded as more sensitive than any other for assessment of renal efficiency. It is simple to perform yet superior to a blood urea estimation alone. Moreover, in some cases of nephritis, diminished urea clearance values may be found, when the blood urea concentration is within normal limits, though results of this type did not happen to occur within our series. Whenever renal insufficiency was detected by biochemical examinations there was also substantiating evidence from a study of the albuminuria itself or of the urinary micro-deposit. However, it is evident from Table 3 that Case 4 might easily have been passed as a persistent albuminuria (without nephritis) if the biochemical tests had been omitted, and the few red corpuscles in the micro-deposit not accorded any significance. Similarly, Case 5 might have appeared to be a postural albuminuria had the biochemical tests been omitted and the micro-deposit overlooked.

Although in our series of patients with simple persistent albuminuria no instances of renal functional impairment were discovered by biochemical examinations, persistent albuminuria was invariably regarded with suspicion and the possibility of renal disease carefully considered. An illustration of the correctness of this view is a case described by Brown and Ginsberg[6] of a woman who had perennial albuminuria for 46 years after scarlet fever at the age of 9. She died at age 55 of left ventricular failure and chronic glomerulonephritis was demonstrated at autopsy.

Conclusions. It is thus concluded that while a persistent albuminuria together with an abnormal urinary deposit provides immediate evidence of renal disease, an albuminuria significant of organic disease may show considerable variation with changes in posture. Determinations of the protein content of the urine are valuable in studying these changes but the protein concentrations themselves possess no diagnostic significance.

When a patient shows any degree of albuminuria in the recumbent position or shows a micro-deposit which is at all suspicious, a urea clearance test may provide further evidence of disease and its performance is therefore advisable. The result of such

† Urea clearance values in brackets are not significantly diminished.

a test, in conjunction with the albuminuria and microscopic evidence, will reveal the occasional case of renal disease which may otherwise go undiscovered. On the other hand, when a proteinuria of postural type is definitely demonstrated and the urinary deposit is above suspicion, renal function tests are not necessary for they will not contribute any indication of kidney disease.

Summary. Previous studies of albuminuria, its types, origin and significance are briefly reviewed in historical perspective.

A laboratory investigation of 193 cases of symptomless albuminuria is recorded, the subjects being referred from primary routine medical examination for recruitment into the Services.

A determination of the type of albuminuria and the nature of the micro-deposit is shown to afford a means of selecting those cases in which the urea clearance test is also likely to be of value.

It is concluded that this scheme of investigation provides the evidence necessary for the medical grading of individuals who have albuminuria but otherwise appear clinically to be healthy.

REFERENCES

1. **Ahronheim, J. H.:** War Medicine, **5**, 267, 1944.
2. **Annotation:** Brit. Med. J., **1**, 269, 1945.
3. **Bashford, H. H.:** Lancet, **2**, 1304, 1926.
4. **Beaumont, G. E.,** and **Dodds, E. C.:** Recent Advances in Medicine, p. 34, 9th ed. London, Churchill, 1939.
5. **Becquerel, L. A.:** Séméiotique des Urines, p. 394. Paris, Fortin, Masson et cie., 1841.
6. **Brown, C. L.,** and **Ginsberg, I. W.:** Arch. Path., **30**, 108, 1940.
7. **Collier, W.:** Trans. Med. Soc. Lond., **30**, 75, 1906-07.
8. **Diehl, H. S.,** and **McKinlay, C. A.:** Arch. Int. Med., **49**, 45, 1932.
9. **Dukes, C.:** Brit. Med. J., **2**, 848, 1905.
10. **Dukes, C. E.:** Urine Examination and Clinical Interpretation, London, Oxford University Press, 1939.
11. **Fox, R. H.:** Lancet, **1**, 116, 1921.
12. **Gulland, G. L.:** Brit. Med. J., **1**, 363, 1927.
13. **Jehle, L.:** Ergebn. d. inn. Med. u. Kinderh., **12**, 808, 1913.
14. **King, E. J., Haslewood, G. A. D.,** and **Delory, G. E.:** Lancet, **1**, 886, 1937.
15. **Leading article:** Lancet, **2**, 566, 1945.
16. **Lee, R. I.:** Med. Clin. N. Am., **3**, 1059, 1920.
17. **von Leube, W.:** Virchows Arch. f. path. Anat., **72**, 145, 1878.
18. **Lyall, A.:** Brit. Med. J., **2**, 113, 1941.
19. **MacLean, H.:** Med. Res. Council, Great Britain, Spec. Report No. 43, 1919.
20. **McLeod, J. W.,** and **Ameuille, P.:** Lancet, **2**, 468, 1916.
21. **Moxon, W.:** Guy's Hosp. Rep., **23**, 233, 1878.
22. **Pavy, F. W.:** Lancet, **2**, 706, 1885.
23. **Post, W. E.,** and **Thomas, W. A.:** J. Am. Med. Assn., **80**, 293, 1923.
24. **Russell, J. W.:** Lancet, **2**, 683, 1925.
25. **Schlutz, F. W.,** and **Swanson, W. W.:** J. Am. Med. Assn., **87**, 1193, 1926.
26. **Senator, H.:** Deut. med. Woch., **30**, 1833, 1904.
27. **Stirling, A. W.:** Lancet, **2**, 1157, 1887.
28. **Teissier, L. J.:** Semana méd., **19**, 425, 1899.
29. **Theobald, G. W.:** Lancet, **2**, 1380, 1932.
30. **Vogel, J.:** Krankheiten der harnbereitenden Organe, Virchow's Handb. d. spez. Path. u. Ther., **6** (part 2), 522, 1864.
31. **Wolman, I. J.:** Am. J. Med. Sci., **210**, 86, 1945.
32. **Young, H. H.: Haines, J. S.,** and **Prince, C. L.:** Mil. Surg., **92**, 353, 1943.

ACRONECROSIS DUE TO FIBRIN THROMBI AND ENDOTHELIAL CELL THROMBI

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Cyanosis followed by necrosis of the extreme parts of the periphery ("Acra") such as the tip of the nose, the lobe of the ear or the tip of a finger, is an event well known to occur in subacute bacterial endocarditis. It is suggested that the term "Acronecrosis" be adopted to describe this phenomenon. Its usual explanation by embolism from distant sites appears to be unsatisfactory in many cases in the light of the findings recorded in this paper. These findings concern locally arising fibrin *thrombi* in post-capillary vessels as observed in 2 such cases. A comparison will be made with the vascular changes in 3 other cases: 1 of subacute bacterial endocarditis without acronecrosis, 1 of unexplained purpura and 1 of fulminant tuberculous septicemia. Finally, the relationship will be discussed with a variety of mural changes in smaller vessels as seen in generalized diseases such as Dermatomyositis, Lupus erythematosus disseminatus and Polyarteriitis nodosa.

Case Abstracts. CASE 1. A man aged 39, 5 years ago, had subacute rheumatic fever. It involved most joints and followed on tonsillitis. One year ago, he had sudden severe pain in left knee; 3 months ago shingles in right leg and pain, while rash was present. Since then, general weakness and development of clinically typical subacute bacterial endocarditis, the most striking feature of which was the symmetrical spread of small hemorrhages with necrotic centers in both ears, right arm, shoulders and big right toe; that is, the picture of "*Acronecrosis*".

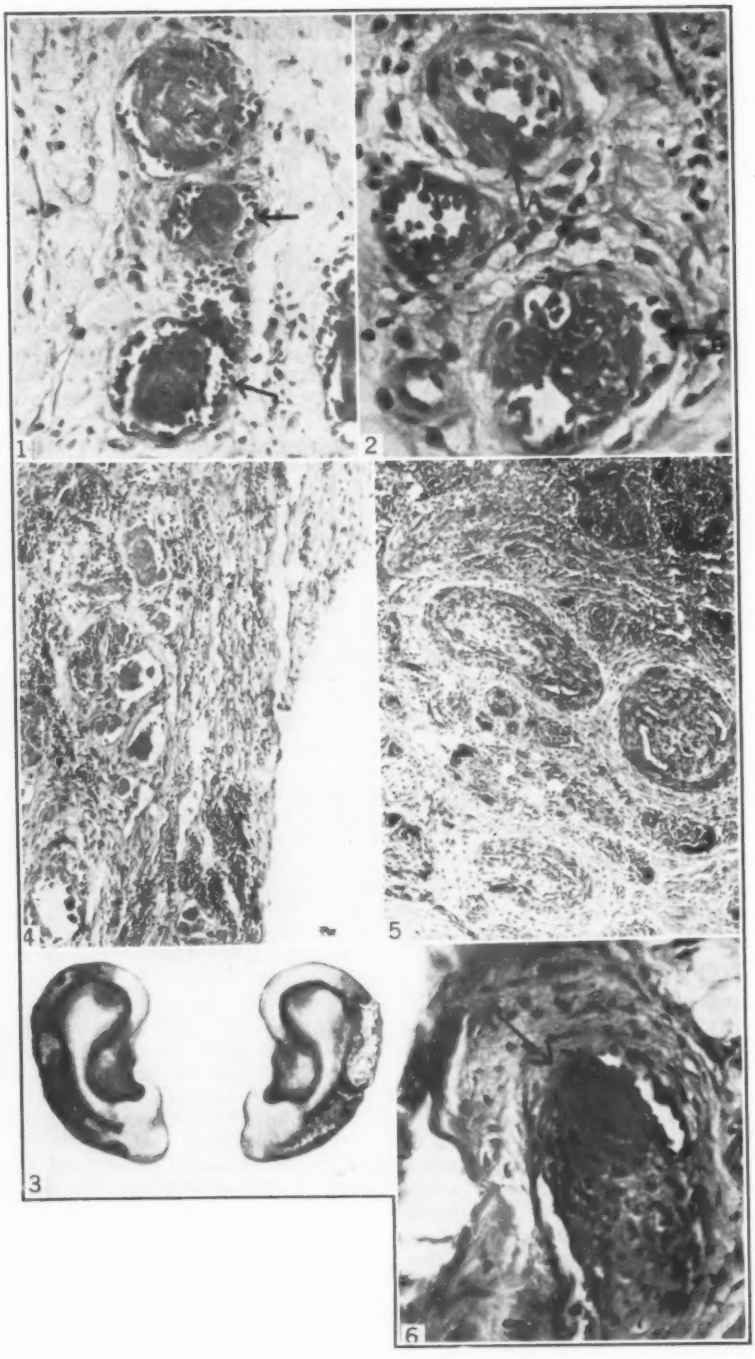
Biopsy No. S.D. 1988 **Skin** (from necrotic area) of 1 finger of the right hand: In the cutis many dilated capillaries and venules are filled with thrombotic material (Fig. 1), the latter usually forming projections of fibrinoid material into the lumen rather than occluding plugs. Sometimes the clot, whether or not endothelialized, bridges the whole lumen effecting partition, or adheres to a thickened intima in which endothelial elements appear to be swollen and proliferating (Figs. 1 and 2). Some of the fibrin-thrombi show an admixture of what appears to be proliferating and desquamated endothelial elements and mononuclear cells.

In one vessel, which is horseshoe shaped in cross section, fibrinoid material lines the entire convex surface.

Necropsy No. 43-221. Irregularly distributed petechiae, notably in the skin of the right hand (including fingers), at the right fore-arm, right toe and in both ear lobes. *Larynx:* Edema and petechiae in the region of left part of the ventricular and vocal cord. *Heart:* Small area of granular vegetations on lateral cusp of tricuspid valve. *Mitral valve:* Two areas, each 2 x 1 cm., of grape-like vegetations. Parietal endocarditis on posterior wall of left ventricle. *Spleen:* Enlarged (14 x 8 x 5 cm.). Almost fluid, dark red on cut section and adherent to adjoining organs. *Kidneys*: 14 x 8 x 44 cm. Capsule strips easily. Surface variegated, with petechiae—the picture of "focal embolic nephritis".

Bacteriology: Spleen grew H. influenzae pure culture.

Histology: *Myocardium:* 1, large fibrotic scars; 2, extensive parietal thrombosis; 3, formations of granulomata in the parietal endocardium beneath the thrombus, with large mononuclear elements, not unlike those seen in Aschoff nodules; 4, almost all the arterioles contain thrombotic material. While in the majority of vessels this material completely plugs the lumen or lies free in its centre, in a few arterioles the clot is eccentrically placed, occupying less than two-thirds of the lumen and fused with the vessel wall. Sometimes there is endothelial cover, but no ingrowth of endothelial cells to suggest that organization has led to the parietal adhesion. *Peripheral Muscle:* Areas of vacuolar degeneration of muscular substance with prolifera-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tion of muscular repair cells forming granulomata. *Kidney:* Fibrinoid conglutination of segments of glomerular tufts and also of afferent arterioles, as seen in "embolic focal nephritis". Some interstitial hemorrhages. *Spleen:* Small area of hemorrhagic necrosis. necrosis.

Comment on Case 1. With regard to the skin changes, the following features are noteworthy: 1, Symmetrical distribution in both ear lobes and shoulder regions; 2, The predilection of lesions for "Acra"; that is, areas in the extreme periphery where circulatory stagnation is most likely to obtain. On clinical grounds alone, therefore, the usual explanation of the small hemorrhages and areas of necrosis in subacute bacterial endocarditis (that is, by embolism), appears unsatisfactory. The fresh granular appearance of the fibrinoid material unaccompanied by organization and yet firmly fused with the vessel wall suggests strongly that this has been a local thrombosis.

CASE 2. Male, aged 30, had rheumatic fever at 6 years with signs of rheumatic carditis until 12.

Latterly developed subacute bacterial endocarditis with slowly progressing hemorrhagic necrosis, affecting the outer fringe of the helix of the ears (Acronecrosis) (Fig. 3). The full details of this case are reported elsewhere (Dr. K. P. Ball).

Biopsy From the Left Ear. (March 27th, 1947; two and a half months before death): The ulcerated area shows fibrinoid necrosis of the upper layer with a fairly sharp lower margin but very little cellular infiltration along the junction line. Deeper, in the surviving tissue, there are nodular perivascular aggregations of lymphocytes. In the living zone, there are many greatly dilated capillaries, some of which contain small projections of endothelial-covered fibrinoid material (Fig. 4), and in a few vessels the lumen is completely filled by the mass.

Necropsy No. 47-205. Tall thin man with slight clubbing of the fingers. No petechiae. There is ulceration of the helix of both ears with some adjacent cyanosis. *Brain:* There is a recent hemorrhagic softening, 1 cm. in diameter, in the right parietal cortex involving the white matter only. There is also a fluid filled space 2 cm. in diameter in the right occipital region. *Heart:* Enlarged, 460 gm. Aortic conus 8 cm. wide. Left ventricle: length from apex to aortic conus 10.5 cm. Left ventricular wall, width 1.3 cm. In the apex and part of the septum there is old and fresh infarction with aneurysmal dilatation. The aortic valve is bicuspid and shows cauliflower vegetations on both cusps, each about 0.5 cm. long. These are hard but easily crumbled. The anterior descending branch of the left coronary artery shows a zone of fibrous narrowing with occlusion about 3 cm. from its origin, but distally the lumen is patent. On the posterior cut surface of the ventricular wall there is myocardial fibrosis.

Histological Examination. *Myocardium:* Some old fibrotic scars and one small area of recent perivascular infiltration with chronic inflammatory cells. *Helix of left ear:* The picture is now quite different from that seen a few weeks before in that the larger (probably arterial) vessels show changes of fibrotic obliteration and recanalization (Fig. 5). The only fibrinoid material seen occurs as small patches enclosed in the fibro-vascular tissue. *Kidney:* Chronic "focal embolic nephritis" with patchy fibrosis of glomeruli.

Comment on Case 2. As in the previous case, the bilateral nature of Acronecrosis and its gradual development argue against an embolic mechanism. Likewise, the histological picture in the biopsy of sessile and polypoid

Fig. 1. Case 1. Capillaries of the skin of finger containing fibrinthrombi, some producing partition of vascular lumen. x 250. In this and subsequent figures, magnifications have been slightly reduced for purposes of reproduction.

Fig. 2. Case 1. Skin. A., a small fibrin thrombus endothelialized and becoming incorporated into the intima simulating fibrinoid infiltration of the latter. B., fibrin thrombus partly endothelialized causing multipartition of vascular lumen. x 375.

Fig. 3. Case 2. Acronecrosis of Helix on both sides.

Fig. 4. Case 2. Biopsy from Helix. Ulcerated area with many venules containing fibrin thrombi being endothelialized. x 100.

Fig. 5. Case 2. Helix. Material removed at autopsy, 10 weeks after biopsy. Picture of organised and recanalised clots. x 90.

Fig. 6. Case 3. Capillary with fibrinoid infiltration of intima. x 375.

projections situated in the venous sinuses points to local formation.

If only material from necropsy had been available, the appearances there of organization and recanalization might well have supported the interpretation of the whole process being the result of previous embolism.

CASE 3. A female factory worker, aged 23, had given up work for 2 years because of ill health. One year before admission she was found to have a presystolic murmur and a radiograph suggestive of mitral stenosis. During the last 3 months, pain in left foot and dyspnea. Obese, cyanosed, young woman, mentally slow. *Fundi:* marked sclerosis of arteries with innumerable petechiae along vessels and papilledema. In right fundus large white-yellow, ? degenerative areas. Gross defects in peripheral areas of fields of vision, complete color blindness. ? Subacute nephritis. Died of heart failure.

NECROPSY 44-103. A very obese, cyanotic and edematous young woman. No changes in brain and pituitary. Tongue smooth. Complete, probably embolic, obstruction of main branch of right pulmonary artery. *Heart* (1000 gm.): Gross dilatation of right side and

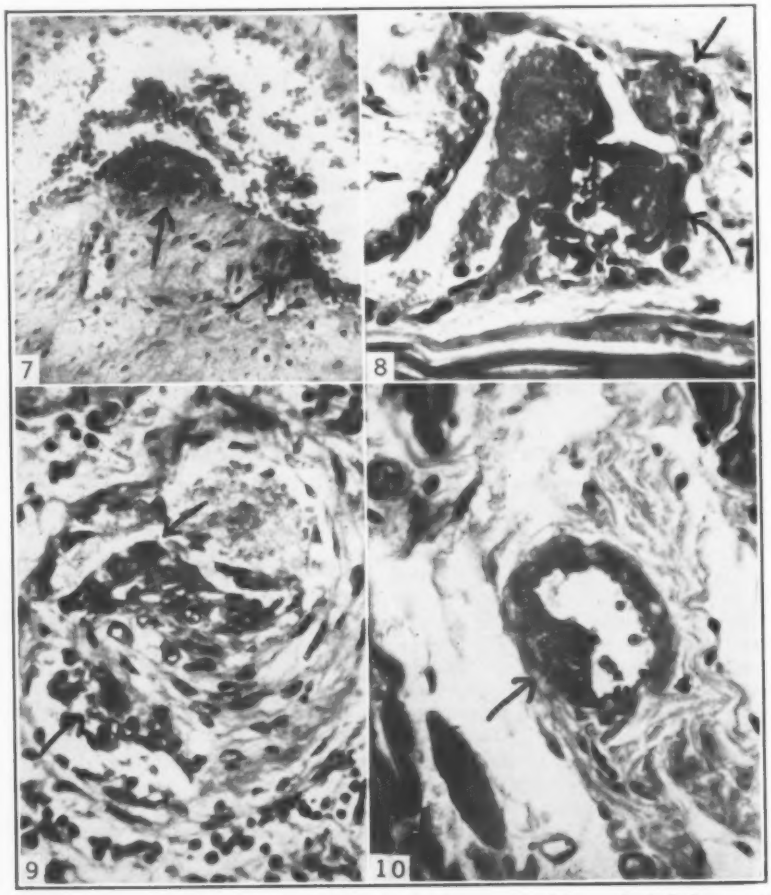

FIG. 7. CASE 3. Lung. 2 small fibrin-thrombi, 1 nearly organized by endothelial syncytia. x 140.
FIG. 8. CASE 3. Heart muscle. Endothelialized fibrin-thrombi with endothelial proliferation. x 600.
FIG. 9. CASE 3. Lung. Bipartite arterial branch with fresh fibrin-thrombi and endothelial cell proliferation. x 620.
FIG. 10. CASE 5. Myocardium. Fibrinoid infiltration of intima. x 500.

auricular appendage filled with thrombotic material. Tricuspid free of vegetation. Posterior cusp of mitral valve covered with easily removable red-currant sized vegetations. Valve itself not thickened or shrunken. Myocardium on cut surface without changes. Aortic valves and aorta free. Right femoral *vein* thrombosed in its whole length. Passive venous congestion of *liver* and *spleen*. From the latter Streptococcus viridans (scanty growth) recovered. *Kidneys:* variegated; picture of a diffuse subacute nephritis.

Histological Examination. *Right auricle:* Some large scars with marked edema. Some medium sized arteries obliterated by recanalized plugs with fibrinoid centres. Myocardium of the *left ventricle:* Precapillary *arterioles* blocked by typical emboli, others by old recanalized plugs, some of which still exhibited fibrinoid patches in the centres. A number of arterioles, however, showed different changes, namely, fibrinoid swelling of the intima at one side or corner of the circumference. In such places the swollen intima protruded into the lumen—not unlike a polypus pushing the endothelial lining forward. In some arterioles, the whole lumen was filled by a hyaline patch with only a few persisting narrow capillary slits.

In these changes 2 processes seem to be involved: 1. Formation of a plug of fibrinoid material which, by organization, becomes part of the vascular wall and subsequently covered by endothelium. 2. Fibrinoid swelling of the vascular wall itself (Figs. 6 and 7). Both these processes were also conspicuous in the tongue, where the frequency of occurrence is second only to the myocardium. Here a stretch of the same vessel may reveal fibrinoid swelling of its wall on one side and a polypoid thrombus narrowing down the lumen on the other. In other small arteries alongside the polypoid mass there is desquamation and proliferation of the endothelium and edematous swelling of the intima (Fig. 8). In the neighborhood of the more superficial vessels of the tongue, the subepithelial collagenous layers show changes which may well be a consequence of the vascular changes. The fibers are separated by edema or show swelling with loss of the usual staining reactions—orange with Mallory or Van Gieson; nonetheless, the argentaffin fibrils are apparently intact. In addition to these focal areas of upset of collagen in relation to affected vessels, there are throughout the body, strikingly so in the diaphragm, larger ill-defined zones of damage to collagen.

Gross changes were also observed in the finer branches of the *Pulmonary Artery*. These were: 1, *Old* changes showing the peculiar partitioning of the lumen as seen in late rheumatic arteriitis (Von Glahn and Pappenheimer[4], 1926); in this 2 or more, and up to 7, lumina are formed by intimal septa from the subendothelial layers while the internal elastic membrane remains apparently unaltered (Fig. 9). In addition, there are frank organized clots projecting like polypi in the larger arterial branches. 2, *Fresh* changes, namely circumscribed fibrinoid swelling of the intima associated with proliferation of peculiar large cells, probably endothelial (Fig. 9). Such swellings and proliferation of cells are particularly evident where the fresh lesion occurred on top of the old changes inside the partitioned lumen of the artery.

In the kidneys some glomeruli exhibited crescents typical of subacute glomerulonephritis, others the "wire loop" pattern as described in Lupus Erythematosus (Klemperer *et al.*[5], 1941).

Comment on Case 3. The various histological changes observed in this case can be traced back to; *a*, lesions of the intima, namely, a plaque-like fibrinoid swelling in the wall which usually occurs on only one side of the vessel. This intimal lesion is most severe in the arterioles of the myocardium, tongue and lungs; *b*, small projecting cushions or polyps of the intima, usually with a core of fibrinoid material and an associated desquamation or proliferation of the endothelium.

CASE 4. Woman aged 74 years. Weakness for a month; for 3 or 4 days purple spots on arms and legs. Admitted comatose. Obese jaundiced woman with stertorous breathing. Blood platelets, 60,000; Hemoglobin, 50%; red blood cells 3,060,000 per c. mm.; white blood cells, 14,500 per c. mm. Diagnosis: Thrombocytopenic purpura.

Necropsy 44-125. Stout old woman with generalized purpuric eruption. Small hemorrhage, 2 x 1 cm., in left *cerebellar cortex*. Confluent bronchopneumonia in right lower and middle lobe. Flabby myocardium, no valvular changes. Atrophic gastric mucosa. Small rusty colored *liver*. Large soft *spleen*, pattern invisible on cut surface. Femur marrow soft, hyperplastic, raspberry colored. *Kidneys:* no appreciable naked eye changes.

Histological Examination. *Heart:* In addition to old triangular scars, extensive changes are found in the small arteries and arterioles. These show hyaline thickening of

the intima, as a rule on one side of the circumference only. There were hardly any additional perivascular changes.

The other organ in which similar vascular changes are most prominent is the *suprarenal*, including the surrounding fat tissue. Not only fresh hyaline infiltration of the intima (chiefly on one side of the vascular circumference), but also fibrous intimal cushions are present, obviously the end result of intimal granulomata, and finally arteries with a double lumen not unlike those found in the lungs of Case 3. The *spleen* and *kidneys* both show hyaline deposits in the intima of the arterioles and there is some hyaline thickening of glomerular capillaries with occasional crescents.

Hemorrhages in the *skin* and *brain* were extensive, but no vascular changes comparable to those described above were discovered. The active femur marrow contained a considerable number of apparently normal megakaryocytes.

Comment on Case 4. This is a case of purpura associated with widespread arteriolar disease without obvious cause. The picture differed from that of the preceding cases in the absence both of fibrinoid infiltration and of valvular vegetations as a possible source of emboli.

CASE 5. Male, aged 54. An instance of fulminant tuberculous septicemia reported in detail elsewhere (Blair and Pagel[1], 1947) This case is mentioned because the arterial capillaries of the myocardium show fibrinoid infiltration involving the intima on one side of the vascular circumference (Fig. 10). These changes are identical with those observed in Case 4 and some of those in Case 3.

The localization of the arteriolar changes in the myocardium in the absence of clinical hypertension or any vascular changes in kidney, spleen or pancreas seem to indicate similarity with the previous cases.

Discussion. The vascular changes in these cases are of 2 types: 1, Small fibrinocellular thrombi found in venules of the skin and occasionally in arterioles, notably of the lung. In the skin the thrombi had caused multipartition of some of the venules. It is reasonable to assume that a similar process can take place in small arteries of the lung with the final result of a picture not unlike the "specific lesions of peripheral blood vessels in rheumatism" described by von Glahn and Pappenheimer[4] (1926). 2, A hyaline-fibrinoid infiltration in the intima of arterioles.

Type 1 is suggested as the explanation accounting for at least some of the cases of "acrocyanosis" and "acronecrosis" in subacute bacterial endocarditis. This type corresponds exactly with the lesions described by Oppenheim[9] (1921) and Ceelen[2] (1926) in typhoid fever, by Siegmund[11,12] (1923, 1925) in a variety of spontaneous (notably streptococcal) and experimental infections and by Pagel[10] (1926) in tuberculosis of the experimental animal. Their experimental reproduction by repeated intravenous administration of microorganisms (staphylococci, B.coli, typhoid or tubercle bacilli) which are, however, not demonstrable in the vascular lesion, suggests that they are connected with a bactericidal and cleansing action situated in the endothelium. Later, the small thrombi are organized, forming intimal granulomata and finally scars. In typhoid fever and tuberculosis it is possible to find a range of vascular lesions, focal necrosis, fibrinoid and monocytic thrombi, intimal granulomata and scars. In subacute bacterial endocarditis the association of fibrinoid thrombi with numerous large mononuclear cells in the capillaries of the extreme periphery such as the ear and fingers is very obvious. This abundance of mononuclear cells may be interpreted as a sequel to the generalized endothelial cell proliferation and the fibrinoid nodules in the peripheral capillaries may also be secondary to endothelial proliferation. It may be mentioned, however, that fibrinoid nodules without associated endothelial proliferation have been produced in the endocardium by the injection of B.coli in vaccinated rabbits (Masugi and Isibasi[7], 1936).

Both the experimental and human

evidence suggest that we are dealing with an immunological phenomenon associated with local fixation and digestion of organisms by endothelial and blood elements. It is suggested that first endothelial cells are destroyed and their debris, together with deposits of fibrinoid material or fibrin, form a small mass adherent to the wall; this is soon endothelialized and organized, to give the intimal granuloma. Where the mass is very small and not projecting it may well give the impression of a fibrinoid thickening of the intima. We thus have a picture not unlike that observed in polyarteritis nodosa, subacute bacterial endocarditis (*e.g.*, Masugi and Isibasi[8], 1937, Fig. 9), disseminated lupus erythematosus (Klemperer *et al.*, 1941), dermatomyositis (Pagel, Woolf and Asher[10a]), and the response to intradermal injection of heat-killed streptococci in rheumatic fever patients (Humphrey and Pagel[4a]). The incorporation of these small fibrinoid masses into the wall is well seen in Cases 1 and 3, and it is only with care that they can be distinguished from the fibrinoid infiltration of the intima seen in Cases 4 and 5. It is, however, not suggested that fibrinoid infiltration of the intima is normally the product of the organization of fibrin thrombi. It is often an independent change and also believed to be of immunological origin (Masugi and Isibasi[8], 1937).

Finally, the location of the fibrin thrombi in extreme parts of the periphery ("Acra"), as seen in Cases 1 and 2 may be explained by a predisposition of these parts to thrombosis, as seen for example, in frostbite, in which hyaline and agglutinated thrombosis is the essential change (Lange, Weiner and Boyd[6], 1946; Friedman and Kritzler[3], 1947).

Summary and Conclusions. 1. In two cases of subacute bacterial endocarditis small fibrin thrombi and endothelial cell thrombi in the venous sinuses of the skin are described as the cause of Acronecrosis.

2. Similar fibrin thrombi and endothelial cell thrombi were observed in the smaller branches of the pulmonary artery in a third case of subacute bacterial endocarditis.

3. Organization of fibrin thrombi and endothelial cell thrombi can lead to fibrinoid and hyaline thickening of parts of the vascular wall or to multipartition of a vessel owing to organization of multiple such thrombi.

4. Necropsy and experimental evidence suggest that the vascular changes described are due to a hyperergic response to antigenic stimuli.

The author's thanks are due to Drs. H. Joules, J. Sakula and K. P. Ball for the clinical notes and helpful suggestions, to Professor A. C. Lendrum for revision of the manuscript, to Mrs. H. Meyer, Mr. J. E. Mayhew and L. Spain for technical and to Miss H. Saxl and Mrs. B. Burnett for photographical assistance.

REFERENCES

1. **Blair, E. J.,** and **Pagel, W.**: Tubercle, **28**, 115, 1947.
2. **Ceelen, W.**: Verh. deut. path. Ges., **21**, 415, 1926.
3. **Friedman, N. B.,** and **Kritzler, R. A.**: Am. J. Path., **23**, 173, 1947.
4. **Von Glahn, W. C.,** and **Pappenheimer, A. M.**: Am. J. Path., **2**, 235, 1926.
4a. **Humphrey, J. H.,** and **Pagel, W.**: Brit. J. Exp. Path. In Press.
5. **Klemperer, P., Pollack, A. D.,** and **Baehr, G.**: Arch. Path., **32**, 569, 1941.
6. **Lange, K., Weiner, D.,** and **Boyd, L. J.**: New England J. Med., **137**, 383, 1947.
7. **Masugi, M.,** and **Isibasi, T.**: Beitr z. path. Anat., **46**, 391, 1936.
8. **Masugi, M.,** and **Isibasi, T.**: Trans. Path. Soc. Japan, **27**, 377, 1937.
9. **Oppenheim, F.**: Centralbl. f. allg. Path. and path. Anat., **31**, 313, 1921.
10. **Pagel, W.**: Verh. deut. path. Ges., **21**, 347, 1926.
10a. **Pagel, W., Woolf, A. L.,** and **Asher, R.**: J. Path. and Bact. In Press.
11. **Siegmund, H.**: Verh. deut. path. Ges., **19**, 114, 1923.
12. Ibid.: **22**, 260, 1925.

THE ADMINISTRATION OF HISTAMINE DURING PREGNANCY: APPARENT LACK OF A CLINICAL OXYTOCIC EFFECT WITH SMALL DOSES

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In the course of a prolonged program of clinical investigation and treatment of the so-called vascular diseases, allergic diseases and certain atypical pain patterns not amenable to more usual forms of treatment, we have had occasion to administer or to prescribe the administration of histamine in relatively small doses by the intravenous or subcutaneous route to 15 pregnant women. The question of the wisdom and the safety of using this drug in pregnancy has arisen. It has been pointed out that not only was histamine first derived from ergot but, in the past, it has actually been used as a uterine stimulant. In addition, the recent obstetric[9], physiologic[26,32], pharmacologic[5,31] and endocrinologic[30] literature continues to discuss the oxytocic effect of histamine in women and in female animals. As recently as 1946, editorial comment in the "Obstetrical and Gynecological Survey" was a reminder that histamine "exerts a powerful stimulating effect directly on the myometrium." Indeed, an impressive array of experimental literature may be found to document this opinion. In view, therefore, of the theoretical and apparent hazards of histamine therapy during gestation, and because of the absence of any undesirable sequelae of such treatment in our series of cases, we wish to record our observations. In addition, we wish briefly to review some of the significant contributions of earlier workers relating to the oxytocic effect of histamine and to the general concept of histamine metabolism in pregnancy. Such data, to our knowledge, have not been gathered together in any recent review. This material will serve as a convenient prologue to our clinical notations.

Review of the Literature. Hofbauer[13] in 1926 studied the effects of acute histamine poisoning in pregnant guinea pigs. He observed a number of phenomena that were similarly noted in premature separation of the normally implanted placenta. Uterine spasm was one of the most consistently observable responses.

Bourne and Burn[4], in 1927, by utilizing intra-uterine bags with manometer attachments in parturient women, demonstrated that histamine injected subcutaneously in a dose of 2.0 mg. (reckoned in terms of histamine base present) produced powerful but short-lived uterine contractions. With doses of less than 1.0 mg., no certain change in the intensity of the uterine movements was seen but an increase in the frequency of the contractions for a period of 30 minutes was encountered. It seemed as though the dose of 2.0 mg. exhausted the uterine musculature, because a period of quiescence followed the heightened

activity, and the effect, powerful as it was, did not shorten the course of labor. The dilatation of the cervical os was not greater at the end of the effect than at the beginning. The effect of the injection of a dose of 2.0 mg. appeared within 1 minute and the intra uterine pressure rose to 76 mm. of mercury and did not fall again to the base line of 25 to 40 mm. of mercury for 20 minutes. The authors supposed that histamine with its rapid-acting effect and ergotamine with its slower-acting effect might, in combination, represent an effective oxytocic.

In 1930 Feldberg and Schilf[10] reviewed all of the available literature on histamine. They observed that the virgin uterus was especially sensitive to histamine and they quoted Dossena[8] regarding its fleeting effect on excised strips of human uterine muscle. Concerning the use of histamine during labor, Jäger's[16,17] studies were extensively cited. He injected histamine in a dose of 8 mg. both subcutaneously and by the intramuscular route. A contractile effect on the uterus could quickly be detected by abdominal palpation. After several minutes, powerful and frequent pains occurred which seemed, for a time, to hasten the birth process and to cause the uterus to become painful and of a ligneous consistency. However, in several cases, after about half an hour, the cervix seemed less dilated, and effacement appeared to have regressed with actual impediment of labor. Koch[23] said that with doses of 0.5 mg. to 1.0 mg. strong labor pains were produced for 5 to 8 minutes and seemed to hasten labor. He also observed that in the use of histamine in the postpartum period a relaxation effect followed the immediate contractile action. He interpreted this effect as a possible fatigue phenomenon. He actually observed severe atony in the postpartum period when histamine had been used during labor.

Feldberg and Schilf concluded that the use of histamine during labor and immediately after delivery was unsuitable for the following reasons: 1, doses of a high order (8 mg.) lead to unsatisfactory and potentially dangerous side effects; 2, prolonged tonic contractions of the uterus may occur; 3, the cervix in some cases not only does not dilate but may contract; 4, the short-lived contractile effects are followed by relaxation; 5, premature separation of the placenta might be induced.

The same authors, in their chapter on the intoxications of pregnancy mentioned that although most authorities did not accept an anaphylactic theory of premature separation of the placenta, Kämmerer[19] believed that at least some of the lesser symptoms of the toxemias of pregnancy are on an allergy-anaphylaxis (histamine) basis.

Küpper[25] in 1930 discussed the work of Koch and Jäger further. Koch said that he had used histamine as a styptic in cases of severe hemorrhage and that injections of 0.25 to 1.0 mg. of the drug had stopped postpartum bleeding. He further stated that the duration of action of histamine lasted from 10 to 24 hours in some cases. Jäger thought that doses up to 6.0 mg. were without effect but that a dose of 8.0 mg. administered by either the subcutaneous or intravenous route produces powerful effects lasting from 60 to 90 minutes. He referred to the side effects of the larger doses as remarkable and objectionable.

Danforth and Gorham[7] in 1937 reasoned that "since histamine is known to be a powerful oxytocic" determinations of the histaminase content of human placentas would be of interest. Accordingly, by the methods of Best and McHenry, histaminase determinations were made upon 84 human placentas. These investigators observed that an increased concentration of histaminase was to be found in the

placentas of women with inertia and sluggish labors. However, Danforth[6] in a later and more detailed publication stated that although the amount of histaminase in the placenta showed some correlation with the efficiency of uterine contractions, the evidence was not sufficient to warrant a definite conclusion. Among the data denying the hypothesis of a correlative relationship was the conclusion of Marcou[27] who found that the concentration of histamine in the blood declines steadily in the few days before labor and does not return to normal until after delivery, whereas, if histamine were an essential oxytocic and histaminase its essential inhibitor, the converse might be expected. Danforth further observed that it had not been possible to initiate premature labor in guinea pigs or in rabbits by the administration of histamine in physiologic doses. He concluded that it was most likely that the histaminase content of the placenta was in no way related to uterine contractions but could be thought of rather as an index of the amount of active, functioning parenchymatous tissue in the placenta.

Kapeller-Adler and Adler[21], and Kapeller-Adler[20], demonstrated that the histaminase reaction was negative on the serum of nonpregnant women but that in normal pregnancy serum, the histaminase reaction was found to be positive without exception, irrespective of the substrate used. It was observed that in toxemic patients there was considerable histaminuria, or histamine was present in the urine in small traces, or lacking altogether.

Ahlmark[1] (1944) in his classic work stated that histamine has a contractile effect upon the uterus (less pronounced during pregnancy) and that the human placenta contains a considerable amount of histaminase. He observed a considerable increase of enzyme (histaminase) activity during pregnancy from about the seventh week after the last menstrual period. At about this time, the increase in enzyme activity is so great that it is possible to demonstrate the increase from one day to another. During the latter part of pregnancy, the enzyme activity attains about 500 to 1,000 times the normal value.

Koloszynski[24] (1945) found that there was clear evidence of specific histaminase activity in the last 6 months of pregnancy but no evidence of such specific activity in nonpregnant women. This author, however, found no inhibition of histaminase activity in preeclampsia as reported by Kapeller-Adler.

Hofbauer[14] in 1946 reviewed the evolution of the biologic concept of the cause of the late toxemias of pregnancy and discussed the literature on histaminase.

Page[28] has discussed a related topic and expressed the opinion that the histidinuria of pregnancy is due to an inhibition of or interference with the renal tubular mechanisms rather than the result of any hormonal inhibition of hepatic histidase by chorionic gonadotropin, as proposed by Kepeller-Adler.

Rose, Harkness and Forbes[29] confirmed Ahlmark's work regarding the increase in the concentration of plasma histaminase in pregnancy.

Editorial comment in the "Obstetrical and Gynecological Survey" in 1946 regarding the articles of Page and Koloszynski, referred to above, reviewed the implications of the relationship of histidine, histamine and histaminase metabolism in pregnancy. It was pointed out that the evidence for a histaminic cause for eclampsia was certainly inconclusive but that a theory of histamine intoxication in placental abruption was a somewhat more reasonable hypothesis. It was stated that histamine is a potent protoplasmic poison (Hueper and Ichniowski[15]);

that it exerts a powerful stimulating effect directly on the myometrium, and that this amine can produce profound shock and in animal experimentation can produce a good replica of abruptio placentae.

Cushny[5], discussing histamine, said that the stomach, intestines and uterus contract powerfully and may pass into spasm in response to histamine and, as the effect is not counteracted by atropine, it probably arises from direct action on the muscle. The uterus, he said, is exceedingly sensitive to the presence of histamine.

Selye[30] reminded that the musculotropic actions of histamine are so marked that some of them serve as a basis for its bio-assay; that is, contraction of guinea-pig intestine or uterus *in vitro*.

Sollmann[31], in the 1948 edition of his "Manual of Pharmacology," said that, clinically, a hypodermic injection of 0.33 mg. to 2 mg. of histamine produces prompt and powerful but brief stimulation of the parturient or postpartum uterus with spasmodic contraction beginning in 1 or 2 minutes and lasting for half an hour (Bourne and Burn[4]; and Jones and Barlow[18].) He further stated that its use is not satisfactory as it causes undesirable side reactions—marked vasodilatation, rapid pulse, headache and violent vomiting. Sollman made the further reminder that the excised uterus of a woman is also stimulated (Kehrer[22], Guggenheim[12]) as are the uteri of pregnant and nonpregnant cats, rabbits and guinea pigs (Barger and Dale[2]), but the uterus of the rat is relaxed (Fuehner[11]).

Clinical Observations. In the 5-year period ending April, 1948, approximately 4,600 patients have been seen on the service of one of us (B. T. H.) and approximately 70,000 intravenous injections of histamine have been given. In addition, some 30,000 subcutaneous injections of this drug have been administered and approximately 1,200 patients have been instructed in the technic of self-administration of the drug by hypodermic injection. Fifteen of these patients (12 of whom had multiple sclerosis) were pregnant while under our care.

The average age of our pregnant patients was 27 years and only 3 patients were past the age of 30 years. Six of the patients were primigravidas and 9 were multigravidas. Seven patients received subcutaneous injections of histamine daily throughout the entire period of gestation. Intravenous injections of this drug have been given in every month of the pregnancy, and in 2 cases the injections were given at least 3 times weekly throughout the entire third trimester to within 3 days of delivery. In 13 of the 14 cases in which the patients have thus far been delivered, there has been no tendency to premature labor, although labor occurred 2 weeks before the expected date in 1 case (Case 14). Twelve of these 14 patients have had their labor after the expected date of confinement. The greatest number of subcutaneous injections given was an estimated number of 270 to 5 of the 6 patients who said that daily injections were taken during the entire pregnancy. The greatest number of intravenous injections given to any patient was 48.

The maximal amount of histamine given was administered to a primigravida, aged 23 years, who had multiple sclerosis. This patient received 45 intravenous injections, each of which consisted of 2.75 mg. of histamine diphosphate (1.0 mg. of histamine base) during the third, fourth and fifth months of her pregnancy. The patient received approximately 140 mg. of histamine diphosphate during her pregnancy. The average total dose for each patient per pregnancy was about 50 mg. of histamine diphosphate. Four

patients in this series were delivered at the Mayo Clinic.

Only one event which might in any way be construed as representing an untoward effect on the pregnant uterus occurred in the entire series. A primigravida (Case 11, Table 1), aged 29 years, had an episode of slight vaginal bleeding 12 hours after a subcutaneous injection of 0.137 mg. of histamine

TABLE 1.--DATA ON THE SUBCUTANEOUS AND INTRAVENOUS ADMINISTRATION OF HISTAMINE TO PREGNANT WOMEN

Case	Age	Gravida	Para	Diagnosis	Administration of Histamine					Duration of labor, hr.	Lactation	Miscellaneous
					Route	Period of pregnancy	Number of injections	Average dose per injection*, (mg.)	Total dose by each route*, (mg.)			
1	23	I	0	Multiple sclerosis	Intravenous†	3rd, 4th, 5th mo.	45	2.95	123.7	36‡	None	Uterine inertia, grade 2.
					Subcutaneous	Last 4 mo.	120	0.137	16.4			
2	17	I	0	Multiple sclerosis	Intravenous†	Last 3 mo.	48	1.83	87.9	10‡	Adequate 6 wk.	Histamine daily until 4 da. before delivery.
3	23	I	0	Multiple sclerosis	Intravenous†	Last 4 mo.	44	1.83	79.1	12‡	Adequate	Histamine every other day until 3 da. before delivery.
4	23	III	II	Multiple sclerosis	Intravenous†	First 3 mo.	32	0.87	28.1	2	None	Most of intravenous therapy in 1st mo.
					Subcutaneous	1st, 2nd, 9th mo.	24	0.137	3.2			
5	26	II	I	Multiple sclerosis	Intravenous†	2nd, 3rd, 4th mo.	34	0.97	33.1	3	None	
6	32	V	III	Pseudo tumor of brain	Intravenous†	5th mo.	24	2.2	52.9	Caesarean section‡	None	
7	33	V	IV	Multiple sclerosis	Intravenous	First 4 mo.	50§	1.0§	50.0§	-	-	
8	31	III	II	Multiple sclerosis	Intravenous	4th, 5th, 6th mo.	34	1.0§	34§	12	Adequate	Considerable false labor during last 18 da. of gestation.
					Subcutaneous	Entire pregnancy	248	0.11	27.0§			
9	40	I	0	Multiple sclerosis	Subcutaneous	Entire pregnancy	200§	0.137	27.5§	2	Adequate, 3 wk.	
10	25	II	I	Migraine and tension headache	Subcutaneous	Entire pregnancy	270§	0.11	29.7§	10	Adequate	Histamine administered every day during pregnancy, labor and puerperium.
11	29	I	0	Multiple sclerosis	Subcutaneous	Entire pregnancy	270§	0.137	37§	11	Nursing not attempted	Uterine bleeding once after administration of histamine. Month of bleeding not mentioned.
12	26	II	I	Multiple sclerosis	Subcutaneous	Entire pregnancy	270§	0.137	37§	10	Adequate, 36 wk.	
13	28	II	I	Multiple sclerosis	Subcutaneous	Entire pregnancy	270§	0.09	24.3§	-	-	
14	26	I	0	Multiple sclerosis	Subcutaneous	Entire pregnancy	270§	0.137	37§	5‡	Adequate	
15	30	V	III	Migraine and tension headache	Intravenous†	3rd mo.	12	0.57	6.92	¶	-	

* Calculated in terms of histamine diphosphate.
† Intravenous administration of histamine conducted at the clinic.
‡ Patient delivered at the clinic.
§ Approximate dose or number of injections.
¶ Patient not delivered when paper was written.

diphosphate (0.05 mg. of histamine base). The month of the pregnancy in which this bleeding occurred is not known. Since this is one of the smaller amounts of histamine given to any patient in the group, the significance of this bleeding is questionable.

The data regarding these patients are summarized in Table 1. The average duration of labor was 12.6 hours for the primigravidas and 7.4 hours for the multigravidas. No postpartum bleeding occurred in this series. The one Caesarean section was done because of a previous Caesarean section. No significant conclusions regarding lactation may be made. However, information is available regarding 12 of the 14 women who have delivered. Four women were unable to nurse their infants; 1 woman did not attempt nursing; 6 women nursed their infants adequately and 1 woman was able to nurse her baby for a period of 3 weeks. It is an interesting, but certainly not statistically significant, sidelight that the 2 women who received intravenous injections of histamine at least 3 times per week throughout the entire third trimester to within 3 days of delivery and were then delivered under our care had bountiful supplies of milk. All of the babies thus far delivered have been normal.

One additional comment may be made regarding the women who received intravenous injections of histamine regularly throughout the third trimester. It was distinctly observed by the technicians and attending physicians that the histamine tolerance of these women, as indicated by their susceptibility to ordinary therapeutic doses of the drug and by the intensity of their histamine flush, was distinctly lowered very shortly after the termination of their pregnancy. The thought is thus advanced that the elevated concentration of histaminase of late pregnancy may well have inhibited the intensity of the cutaneous flush and other systemic side effects of histamine in the terminal stages of pregnancy, for similar doses of histamine could not be tolerated in the immediate puerperium.

Comment. We wish to suggest on the basis of our experience that there is at least an apparent lack of a clinical oxytocic effect when the mentioned therapeutic doses of histamine diphosphate are administered by the subcutaneous or intravenous route or by both routes to pregnant women. Zeller[33] has calculated and suggested, on the basis of his data and Ahlmark's data, that one might expect approximately 30 mg. of histamine base per hour to be inactivated by the histaminase (di-amine oxidase) present in approximately 5,000 cc. of blood of a pregnant female near term, and, therefore, that the amount of histamine which we have administered might, on theoretical grounds, be regarded as a nonoxytocic dose. (The blood volume[3] of an average sized male [70 kg.] is about 6,300 cc.)

We offer no preferred explanation as to why the oxytocic effect described by so many authors and attested by abundant laboratory study did not occur. Our only purpose has been to express the physiologic point that these relatively small doses of histamine did not elicit, from our patients, a clinically measurable uterine response. However, a few of the possibilities which immediately present themselves to explain the theoretical discrepancies are: 1, that the elevated concentration of histaminase known to occur in pregnant women might be responsible for the inactivation of the injected histamine (see Zeller's calculation previously mentioned); 2, that the dose of histamine used was not adequate to provoke a clinically observable oxytocic response (the workers who administered histamine as an oxytocic used some doses of a much higher order than ours); 3, that the altered neurogenic response in the 12 patients in

this series who had multiple sclerosis may in some way, in these patients, have altered the predicted effect.

Summary. Various authors have stated that histamine has an oxytocic effect on women and female animals. We have had occasion to prescribe the administration of histamine diphosphate in relatively small doses by the intravenous or subcutaneous route to 15 pregnant women. In only one instance was there possibly an untoward effect: a primigravida, aged 29 years, had slight vaginal bleeding 12 hours after a small subcutaneous dose, 0.137 mg. This was one of the smallest doses of the drug administered in these cases. Postpartum bleeding did not occur in any of the cases. We can offer no explanation as to why the oxytocic effect described by many authors and attested by abundant laboratory study did not occur in any of the 15 cases in our series.

REFERENCES

1. **Ahlmark, A.:** Lancet, **2**, 406, 1944.
2. **Barger, G.,** and **Dale, H. H.:** J. Physiol., **40**, xxxviii, 1910; and Proc. Chem. Soc., **26**, 128, 1910. (Quoted by Sollmann[31]).
3. **Best, C. H.,** and **Taylor, N. B.:** The Physiological Basis of Medical Practice, 2d ed., p. 26, Baltimore, Williams & Wilkins, 1939.
4. **Bourne, A.** and **Burn, J. H.:** J. Obst. and Gyn. Brit. Emp., **34**, 249, 1927.
5. **Cushny, A. R.:** Pharmacology and Therapeutics, 13th ed., p. 523, Philadelphia, Lea & Febiger, 1947.
6. **Danforth, D. N.:** Proc. Soc. Exp. Biol. and Med., **40**, 319, 1939.
7. **Danforth, D. N.,** and **Gorham, Frank:** Am. J. Physiol., **119**, 294, 1937.
8. **Dossena, G.:** Ann. di Ostet., **50**, 1379, 1928. (Quoted by Feldberg and Schilf[10]).
9. Editorial Comment on Kolozynski, E. W.: A Short Study of Histaminase Activity During Pregnancy, and on Page, E. W.: The Mechanism of the Histidinuria of Pregnancy. Obst. and Gyn. Surv., **1**, 301, 1946.
10. **Feldberg, W.,** and **Schilf, E.:** Histamin; seine Pharmakologie und Bedeutung für die Humoralphysiologie, Berlin, Julius Springer, 1930.
11. **Fuehner, H.:** Therap. Monatschr., **27**, 202, 1913. (Quoted by Sollmann[31]).
12. **Guggenheim, M.:** Therap. Monatschr., **28**, 174, 1914. (Quoted by Sollmann[31]).
13. **Hofbauer, J.:** Am. J. Obst. and Gyn., **12**, 159, 1926.
14. Ibid.: **51**, 514, 1946.
15. **Hueper, W. C.,** and **Ichniowski, C. T.:** Am. J. Path., **20**, 211, 1944, and quoted in Editorial Comment[9].
16. **Jäger, F.:** Münch. med. Wochn., **2**, 1714, 1913.
17. Idem: Zentralbl. f. Gynäk., **37**, 265, 1913.
18. **Jones** and **Barlow:** (Cited by Sollmann, Torald[31], but reference not given).
19. **Kämmerer, Hugo:** Allergische Diathes und Allergische Erkrankungen, München; J. F. Bergmann, 1926. (Quoted by Feldberg and Schilf[10]).
20. **Kapeller-Adler, R.:** Biochem. J., **38**, 270, 1944.
21. **Kapeller-Adler, R.,** and **Adler, E.:** J. Obst. and Gyn. Brit. Emp., **50**, 177, 1943.
22. **Kehrer:** Verch. d. dent. Ges. f. Gyn., **14**, 360, 1911. (Quoted by Sollmann[31]).
23. **Koch, C.:** Zentralbl. f. Gynäk., **37**, 564, 1913.
24. **Koloszynski, E. W.:** J. Obst. and Gyn. Brit. Emp., **52**, 486, 1945.
25. **Küpper, Anton:** Ergebn. d. Physiol., **30**, 153, 1930.
26. **McDowall, R. J. S.:** Handbook of Physiology and Biochemistry, 39th ed., p. 793. Philadelphia, Blakiston, 1946.
27. **Marcou, L.,** and **Atanasiu-Vergu:** Quoted by Danforth, D. N.[6]
28. **Page, E. W.:** Am. J. Obst. and Gyn., **51**, 553, 1946.
29. **Rose, B., Harkness, E. V.,** and **Forbes, R. P.:** 1946 Ann. Rep. John and Mary R Markle Foundation., 69, 1947.
30. **Selye, Hans:** Textbook of Endocrinology, p. 789., Montreal, Université de Montréal, 1947.
31. **Sollmann, Torald:** A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology. 7th ed., p. 411, Philadelphia, W. B. Saunders, 1948.
32. **Wright, Samson:** Applied Physiology, 8th ed., p. 556, New York, Oxford University Press, 1945.
33. **Zeller, E.:** Personal communication.

THE ABSORPTION, DISTRIBUTION, EXCRETION AND TOXICITY OF BACITRACIN IN MAN* †

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Since the original description of bacitracin[5] by Johnson, Anker and Meleney, a number of articles have appeared in the literature regarding the characteristics of bacitracin, the pharmacology of bacitracin in animals and the clinical effectiveness of bacitracin in the treatment of clinical infections in man[1-4,6,7,9-12]. As the clinical results have in large part been covered in these publications, no attempt will be made in this report to analyze the clinical results of bacitracin therapy in the 152 patients treated by members of the staff of the Hospital of the University of Pennsylvania. However, the absorption, distribution, toxicity and excretion of commercial preparations of bacitracin were determined in a limited number of patients. An attempt was also made to determine the concentration of bacitracin attained in pleural, ascitic, cerebrospinal and pericardial fluids in respect to the concentration of bacitracin in the blood serum. Studies were also made to determine possible toxic effects on the liver, kidney, and the cellular elements of the blood.

Absorption. The concentrations of bacitracin present in the blood serum 1, 2, 4 and 6 hours after an initial intramuscular injection of bacitracin were determined in 33 patients. The dosages used varied between 16,000 and 60,000 units of bacitracin. The majority of the patients received 50,000 units of bacitracin intramuscularly every 6 hours. Following a single intramuscular injection of 50,000 units of bacitracin the highest concentration of bacitracin in the serum was usually found 2 hours after the injection. At this interval of time the concentration was usually in the neighborhood of 0.3 units of bacitracin per cc. of serum, although concentrations as high as 1.0 unit and as low as 0.006 units per cc. of serum were observed. Six hours after the injection the average concentration of bacitracin was 0.03 units per cc. of serum with variations between 0.004 and 0.46 units per cc. of serum. After repeated injections of 50,000 units of bacitracin at 6 hour intervals for several days, bacitracin levels, ranging between 1 and 3 units per cc. of serum were frequently found. (See also Tables 1 and 2 and Figs. 1 and 2.) The method of determining the concentration of bacitracin in body fluids was devised by Miss Balbina A. Johnson. No correction was made for the partial inhibition of bacitracin by serum as described by Scudi[11].

* The work decribed in this paper was done under a contract between the Department of the Army and the University of Pennsylvania and was reported to the Subcommittee on Chemotherapeutic and other Agents of the National Research Council on November 22, 1948.

† The Bacitracin was kindly supplied to us by the Commercial Solvents Corporation.

TABLE 1. CONCENTRATION OF BACITRACIN IN BLOOD SERUM AND ASCITIC FLUID FOLLOWING A SINGLE INTRAMUSCULAR INJECTION OF 49,000 UNITS IN 3 AVERAGE CASES

Disease	Hepatic Cirrhosis		Abdominal Carcinomatosis		Gastric Carcinoma	
	Blood Serum	Ascitic Fluid	Blood Serum	Ascitic Fluid	Blood Serum	Ascitic Fluid
1 hr.	0.281	0.0018	0.016	0.005	----	0.002
2 hr.	0.261	0.0281	0.0314	0.004	0.006	0.008
4 hr.	0.841	0.0156	0.128	0.064	0.125	0.062
6 hr.	0.46	0.064	0.064	0.128	0.031	0.062

TABLE 2. CONCENTRATION OF BACITRACIN IN BLOOD SERUM AND SPINAL FLUID FOLLOWING THE INTRAMUSCULAR INJECTION OF 49,000 UNITS OF BACITRACIN IN A CASE OF BRAIN TUMOR

Time After Injection	Blood Serum Level	Spinal Fluid Level
	u/cc.	u/cc.
1 hr.	0.12	0.0009
2 hr.	0.25	0.004
4 hr.	0.03	0.007
6 hr.	0.03	0.004

DISTRIBUTION. Bacitracin was readily distributed to pleural and ascitic fluids. Only traces of bacitracin were found in pericardial and cerebrospinal fluids. The concentrations of bacitracin found in blood and pleural fluid at intervals over a period of 6 hours following a single intramuscular injection of 40,000 units of bacitracin to a patient with arteriosclerotic heart disease and myocardial infarction are shown graphically in Fig. 1. In this patient the pleural fluid concentration of bacitracin gradually increased until at the end of 4 hours it was equal to the then falling concentration of bacitracin in the blood serum. The concentrations of bacitracin in the blood serum and ascitic fluid following a single intramuscular injection of 49,000 units of bacitracin in a patient with abdominal carcinomatosis are shown in Fig. 2. The concentration of bacitracin in the ascitic fluid gradually increased until it was greater than the concentration of bacitracin in the serum 6 hours after the injection of the bacitracin. Table 1 shows the marked variations that occur in the bacitracin concentrations attained in ascitic fluid as compared to the serum

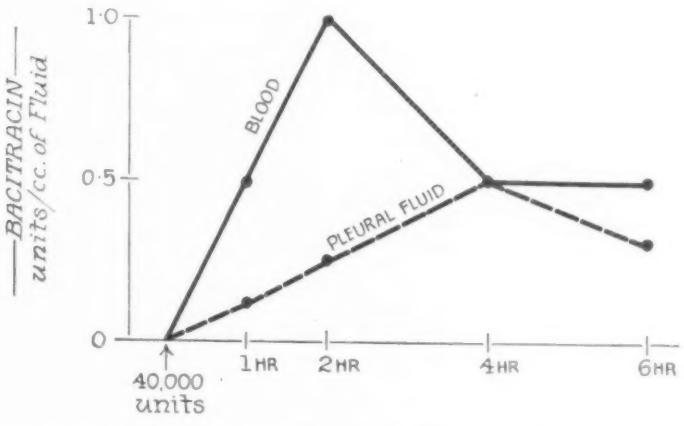

FIG. 1. Concentration of bacitracin in blood and pleural fluid following a single intramuscular injection of 40,000 units in a patient with myocardial infarction.

concentrations following single intramuscular injections of 50,000 units of bacitracin intramuscularly. The concentrations of bacitracin in the ascitic fluid of different patients may vary with the amount of ascitic fluid present and the disease process which produces the ascitic fluid. A patient with a brain tumor had only traces of bacitracin in the cerebrospinal fluid following 1 intramuscular injection of 50,000 units of bacitracin (Table 2). One hour after intramuscular injection of 49,000 units of bacitracin, a patient with tuberculous pericarditis was found to have 0.005 units of bacitracin per cc. of pericardial fluid.

EXCRETION. The urinary excretion of systemically administered bacitracin during the first 24 hours of therapy was studied in 9 patients. The results are shown in Table 3. The total daily dosages varied between 80,000 and 260,000 units of bacitracin (20,000 to 65,000 units intramuscularly every 6 hours). The percentage of the total adminis-

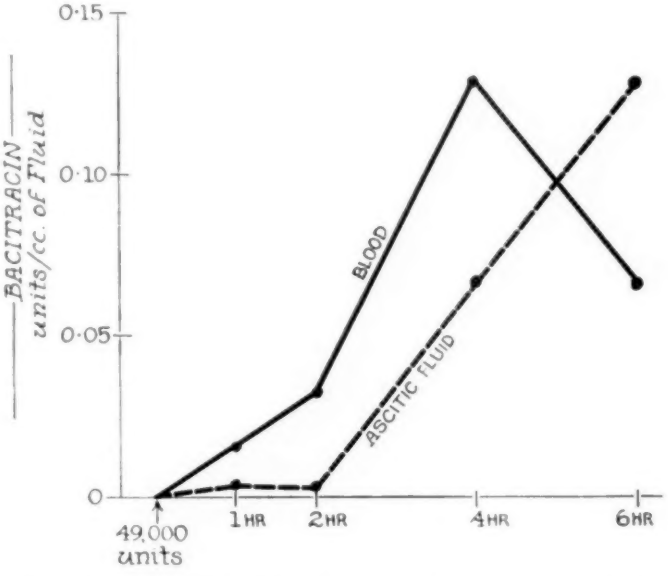

FIG. 2. Concentration of bacitracin in blood and ascitic fluid following a single intramuscular injection of 49,000 units in a patient with abdominal carcinomatosis.

TABLE 3. URINARY EXCRETION OF BACITRACIN, INITIAL 24 HOURS

Patient	Bacitracin Total Daily Dosage u	Daily Urinary Output cc.	Daily Urinary Bacitracin Excretion u	Percentage Bacitracin Excreted %
1	260,000	2,500	50,000	19.2
2	162,000	635	15,325	9.4
3	196,000	1,425	60,712	30.9
4	200,000	775	42,660	21.3
5	216,000	3,060	42,100	19.5
6	209,000	2,050	60,200	28.7
7	196,000	1,575	32,100	16.0
8	80,000	1,320	20,240	25.3
9	200,000	875	24,260	12.1

tered bacitracin excreted in 24 hours varied between 9.4 and 30.9%. It is apparent that considerable bacitracin is either retained or destroyed in the body. The 24 hour urine volumes of these patients varied between 635 cc. and 3,060 cc. of urine. In the data obtained there was no apparent correlation between the 24 hour urine volume and the percentage of the total administered bacitracin that appeared in the urine. In Patients 2 and 9 the 24 hour urinary excretion of bacitracin was again determined after several days of bacitracin therapy and the percent of the total daily dose of the antibiotic excreted was found to be 23.5% and 21.4% respectively.

TOXICITY. The incidence of clinical evidences of bacitracin toxicity in 20 patients who received the antibiotic intramuscularly is shown in Table 4. Although the majority of these patients received approximately 50,000 units of bacitracin every 6 hours or a total daily dose of 200,000 units of bacitracin, several of the patients developed evidences of toxicity on a total daily dose as low as 80,000 units per day.

TABLE 4. CLINICAL EVIDENCES OF BACITRACIN TOXICITY IN 20 PATIENTS

	%
Local pain and induration (7)	35
Local petechiae (1)	5
Skin rash (3)	15
Nausea and, or, vomiting (5)	25
Appearance of albuminuria or increase in albuminuria (5)	25
Ringing in ears (1)	5
"Taste" in mouth (1)	5

The numbers in parentheses indicate the number of cases.

It is difficult to evaluate the degree of local pain experienced by a patient following an intramuscular injection. For the purpose of this evaluation, local pain and induration were considered as evidences of local toxicity only when the patient complained of pain or when obvious induration was present for 24 hours after an intramuscular injection. Procaine solution (0.5%) was used as the diluent for all intramuscular injections. Pain immediately after injection of the procaine-bacitracin solution was minimal.

Petechiae of the skin in the area of an intramuscular injection were noted in 1 patient. Three patients developed an extensive macular skin rash. In 2 instances the rash disappeared during bacitracin therapy. The third patient developed the skin rash 7 days after bacitracin was discontinued. The patient, who developed the skin rash 7 days after discontinuation of bacitracin therapy, received no other chemotherapeutic or antibiotic agents before the rash appeared. The bacitracin was discontinued because of nausea and vomiting, which persisted until the rash appeared.

Nausea or nausea and vomiting were present in 25% of the 20 patients. In several patients it was necessary to discontinue bacitracin therapy because of persistent and severe nausea and vomiting. One patient with osteomyelitis of the spine, received bacitracin on 3 different occasions 3 to 5 weeks apart. There were no evidences of toxicity during the first period of therapy. During the second period of therapy he complained of nausea, ringing of the ears, and immediately after an injection, a peculiar taste in the mouth. The third time that bacitracin was administered the same symptoms were experienced and it was necessary to discontinue bacitracin after 3 days of therapy because of severe nausea and vomiting.

The appearance of albuminuria in patients previously free of albuminuria or an increase in the amount of albuminuria in patients who had albuminuria before bacitracin therapy was started, was noticed in 5 of the 20 patients.

RENAL FUNCTION. Blood urea nitro-

gen determinations were performed in 12 patients before and after bacitracin therapy (Table 5). Although the blood urea nitrogen levels increased in 7 instances and decreased in 5 instances, only in 4 instances were the increases significant. In 3 patients determinations of the phenolsulfonphthalein excretion before and after systemic bacitracin failed to show evidence of kidney damage in 2 of the patients, but did show some evidence of renal damage in the third patient. In this case the blood urea nitrogen rose from 13 to 31 and the 2 hour phenolsulfonphthalein excretion fell from 68 to 40% after the administration of 80,000 units of bacitracin daily systemically for 6 days.

In 10 patients renal function tests were performed before and after bacitracin therapy. The 5 patients who received 196,000 to 200,000 units of bacitracin daily for from 4 to 13 days showed slight to very severe diminution in glomerular filtration rate, renal plasma flow, and maximal tubular excretion of para-aminohippuric acid (Table 6). The changes in renal function were similar to those observed in shock due to severe muscle trauma and severe hemorrhage; and similar to those changes in renal function observed following mercury bichloride, carbon tetrachloride and sulfanilamide poisoning. Five patients who received 23,000 units of bacitracin intravenously for 1 hour, failed to show significant changes in the renal functions determined. Details of the renal function studies are being reported in a separate publication[8].

TABLE 6. AVERAGE DIMINUTION OF RENAL FUNCTIONS AFTER THE SYSTEMIC ADMINISTRATION OF 196,000 TO 200,000 UNITS OF BACITRACIN DAILY FOR 4 TO 13 DAYS IN 5 PATIENTS

	%
Glomerular filtration rate	45.8
Renal plasma flow	49.4
Maximal tubular excretion	61.4
Maximal tubular reabsorption of phosphate	36.2

TABLE 5. BLOOD UREA NITROGEN BEFORE AND AFTER SYSTEMIC BACITRACIN THERAPY IN 12 PATIENTS

No. of Case	Days of Treatment	Total Units of Bacitracin	BUN Before Treatment mg. %	BUN After Treatment mg. %
1	15	3,240,000	15	14
2	24	2,640,000	8	10.5
3	13	2,600,000	17	21
4	10	1,960,000	8	14
5	8	1,760,000	9	33
6	20	1,700,000	8	7
7	7	1,372,000	10	9
8	18	1,368,000	11	13
9	14	1,232,000	15	21
10	7	700,000	8	7
11	8	640,000	13	31
12	1	200,000	21	13
			Average 12.1	15.95

LIVER FUNCTION AND BLOOD CYTOLOGY. Liver function studies were determined before and after the administration of systemic bacitracin to 4 patients. The patients received 50,000 units of bacitracin intramuscularly every 6 hours for from 4 to 10 days. No evidence of hepatic damage following the administration of bacitracin was found as judged by the van den Bergh reaction,

bromsulfalein retention, free and total blood cholesterol, cephalin flocculation, thymol turbidity or colloidal gold reaction. The only variation from normal noted was the change in the cephalin flocculation from zero to plus 2 in 1 patient. The average results of these observations before and after bacitracin are given in Table 7. Ten patients who received 50,000 units of bacitracin intramuscularly every 6 hours for periods of time varying from 3 to 19 days showed no evidence of blood cytology changes after the administration of bacitracin as judged by red blood cell counts and differential white blood cell counts before and after administration of bacitracin.

2. Bacitracin administered systemically is readily distributed to pleural and ascitic fluids.

3. Only traces of bacitracin are found in the cerebrospinal fluid.

4. Nine to 30.9% of the administered bacitracin was recovered in the urine in the initial 24 hour period of therapy.

5. Clinical evidences of the toxicity of the bacitracin preparations which we used for systemic administration were frequently observed. These included local pain and induration, local petechiae of the skin, extensive skin rash, nausea, vomiting, ringing in the ears, and a "taste" in the mouth.

6. Each of the 5 patients, who received from 196,000 to 200,000 units of bacitracin daily intramuscularly for periods of time varying from 4 to 13 days, showed moderate to severe diminution in glomerular filtration rate, renal plasma flow, maximal tubular excretion of para-aminohippuric acid, and maximal tubular reabsorption of phosphate.

TABLE 7. LIVER FUNCTION TESTS BEFORE AND AFTER SYSTEMIC BACITRACIN, AVERAGES IN 4 PATIENTS

	Before	After
Van den Bergh	0.14 mg. per 100 cc.	0.20 mg. per 100 cc.
Bromsulfalein Retention		
5 minutes	2.82 %	1.2 %
30 minutes	0.0 %	0.0 %
Cholesterol		
Total	154.5 mg. per 100 cc.	138.2 mg. per 100 cc.
Free	44.0 mg. per 100 cc.	38.3 mg. per 100 cc.

Cephalin flocculation, thymol turbidity, and colloidal gold tests negative except for a cephalin flocculation change of zero to 2+ in 1 patient.

It is evident that the bacitracin in the form supplied to us and in the dosages used is toxic in man. It is realized that the dosage of 200,000 units per day is larger than most investigators have used. The incidence of clinical evidences of toxic reactions may be high because of the large total daily dosage used in most of these patients, however the same types of toxic reactions were observed on a total daily dose as small as 80,000 units.

Conclusions. 1. Bacitracin blood serum concentrations after a single intramuscular injection of 50,000 units intramuscularly usually reaches a maximum approximately 2 hours after the injection, and there is an appreciable blood bacitracin concentration in the serum 6 hours after the injection.

7. No evidence of liver damage was indicated by the liver function studies employed in 4 patients who received 200,000 units of bacitracin intramuscularly daily for periods varying from 4 to 10 days.

8. No significant changes were noted in the red blood cell counts or the differential white cell counts in 10 patients who received large amounts of intramuscular bacitracin over periods of 3 to 19 days.

REFERENCES

1. **Anker, H. S., Johnson, B. A., Goldberg, J.,** and **Meleney,** F. L.: J. Bacteriol. **55,** 249, 1948.
2. **Eagle, H.,** and **Fleishman, R.:** Ibid., **55,** 341, 1948.
3. **Eagle, H., Musselman, A. D.,** and **Fleischman, R.:** Ibid., **55,** 347, 1948.
4. **Eagle, H., Newman, E. V., Greif, R., Burkholder, T. M.,** and **Goodman, S. C.:** J. Clin. Invest., **26,** 919, 1947.
5. **Johnson, B. A., Anker, H.,** and **Meleney, F. L.:** Science, **102,** 376, 1945.
6. **Meleney, F. L., Altemeier, W. A., Longacre, A. B., Pulaski, E. J.,** and **Zintel, H. A.:** Ann. Am. Surg., **128,** 714, 1948.
7. **Meleney, F. L.,** and **Johnson, B. A.:** J. Am. Med. Assn., **133,** 675, 1947.
8. **Michie, A. J., Zintel, H. A.,** and **Ragni, M.:** The Nephrotoxicity of Bacitracin in Man. To be published.
9. **Miller, J. L., Slatkin, M. H.,** and **Johnson, B. A.:** J. Invest. Derm., **10,** 179, 1948.
10. **Scudi, J. V.,** and **Antopol, W.:** Proc. Soc. Exp. Biol. and Med., **64,** 503, 1947.
11. **Scudi, J. V., Clift, M. E.,** and **Krueger, R. A.:** Proc. Soc. Exp. Biol. and Med., **65,** 9, 1947.
12. **Scudi, J. V., Coret, I. A.,** and **Antopol, W.:** Proc. Soc. Exp. Biol. and Med., **66,** 558, 1947.

PROGRESS
OF
MEDICAL SCIENCE

DERMATOLOGY AND SYPHILOLOGY

UNDER THE CHARGE OF

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DRUG ERUPTIONS: A SURVEY OF RECENT LITERATURE

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THE literature on drug eruptions is so extensive that in this summary we shall aim to touch the high lights of our present knowledge and supply detail in those aspects of the problem which are either new and of practical value or in which we have been personally interested during the past two decades.

From the almost countless sources of information on drug eruptions, certain accessible studies are worthy of note. Among them are the monograph by Prince Morrow[126], J. Jadassohn's early reports[80], R. L. Mayer's[119] contribution to the Jadassohn Handbuch, the various papers by Abramowitz[1a,d,2,3], Fox[56], Wise[201a], Wise and Abramowitz[202], Wise and Sulzberger[203a,b], Sulzberger's "Dermatologic Allergy"[177], Sulzberger and Baer[178], Longcope[107], Brunsting[30], Burgess[31], Kierland and Brunsting[89], Wilson[200b], Urbach and Gottlieb[187], and Sherman[167,168].

By drug eruption is meant a cutaneous or oral mucosal process incident to the administration of drugs, or their split products, which come in contact with the affected part by way of the general circulation. These eruptions may result from medicaments administered by ingestion, injection, inhalation or inunction. Absorption may occur from the skin, urinary bladder, conjunctiva, deep open wounds, vaginal, anal, oral and nasal mucosae, the pulmonary system, mother's milk and transplacentally. In this concept local application of medicaments producing eczematous contact eruptions are excluded. A number of factors are usually recognized as predisposing to these eruptions. Among them are

menses, menopause, pregnancy, other allergic processes, infections, functional states, organic disease, especially liver and cardiorenal, pigmentation or depigmentation (vitiligo), physical factors, sunlight, heat, cold, weather[142], blood groups, vitamins, nutritional states, and personal status of the patient. For example, in our discussion of arsenical reactions[172a,b] we noted the following significant factors in the background of the eruptions (as well as other reactions) produced by this group of drugs: age, sex, race, number of treatments, dosage, type of syphilis, diet, nutritional state, vitamins, nervous reactions, seasons, pregnancy, toxemia of pregnancy, intercurrent infection, and technical elements. In the ensuing discussion only some of the above factors in the predisposing background of certain drug eruptions will be discussed.

Drug eruptions are not rare. While any of the thousands of drugs and chemicals used as medicines may be responsible for drug eruptions, such eruptions are less frequent than eruptions known to be produced by foods[156]. Among 100,000 consecutive general admissions to the University of Kansas Hospital, Sutton[180a] found that the ratio of drug eruptions to all illnesses was 1 to 2000 (0.05%). Of 4000 patients with various dermatoses observed in private practice, the incidence was 1 to 310 (0.32%). Abramowitz[1c] found the percentage among 56,634 admissions at the skin and cancer units of the New York Post-Graduate Hospital during the 5 years 1934-1938 to be 0.15% (1 of 65 patients with other dermatoses). Wise[201a] has summarized the incidence question as follows:

"Important as drug eruptions are, in their relation to every phase of medical practice, their incidence, when compared with the incidence of skin diseases in general, is low; moreover, most of them are mild and of short duration. While many disappear more or less promptly when the offending drug is stopped, a small proportion are of long duration and may coexist with serious impairment of health and curtailment of productive activities; in a still smaller proportion of patients, the prognosis may be quite grave and the disease may be fatal.

"When one reflects on the enormous quantities of hypnotic, sedative, analgesic, cathartic and other medicaments including vitamins, hormones, antibiotics, etc., consumed by the public day in and day out, without causing untoward manifestations except in isolated instances, it becomes evident that hypersensitivity is of relatively rare occurrence. In this connection, it is of interest to note that some textbooks state that eruptions from aspirin are 'common.' This led the author to ask several dermatologists of many years experience how many aspirin eruptions they had encountered; one said 'between 35 and 50,' the other said 'only one.' One of the older general practitioners in New York could recall only one instance, which happened to be fatal and was recorded in the literature; in my experience of 40 years, I have seen only 4 patients with aspirin eruptions. Such a disparity is hard to explain.

"On the other hand, a large number and variety of drugs are significantly prone to induce eruptions showing great variations with respect to clinical symptoms, course, complications, response to therapy, prognosis and so forth. This group comprises for the most part, the iodides and bromides, the antitreponemal arsenicals and bismuth, the various preparations of gold, the sulfonamides and penicillins and atabrine (quinacrine hydrochloride). Some drugs, of which nirvanol, used in the treatment of chorea, is said to be an outstanding example, provoke eruptions in all recipients. Under circumstances in which one or another of this group of drugs is used by *mass-administration,* such as obtains in large hospital wards and clinics devoted to the treatment of venereal diseases, the incidence of drug eruptions is naturally disproportionately high, when compared with their incidence in polyclinics and in private practice. This is true, also, with respect to gold compounds used in arthritis and in lupus erythematosus; perhaps the most significant occurrence, in this connection, is the incidence of eruptions resulting from the mass-administration of atabrine to the armed forces in the Pacific and parts of the Mediterranean areas, for the prevention and treatment of malaria. But even with respect to atabrine reactions in general, Agress found an inci-

dence of less than one-twentieth of one per cent."

The importance of drug eruptions is not reflected in the incidence figures, since we have indicated that the incidence is generally low. Because these eruptions may resemble so many cutaneous diseases of other causation and because persistence in the administration of the particular drug involved might end in disaster[146,153], a thorough knowledge of the diagnostic clinical features of the eruption produced by the various drugs should be clearly understood.

The characteristics of the eruptions of drug allergy have been summarized by Sulzberger[177] as follows:

1. Even very minute amounts of a drug which has been well tolerated for weeks, months, or years may suddenly produce severe eruptions.

2. Once such an eruption has occurred, it is likely to recur upon subsequent minute exposures to the offending drug or to a related drug.

3. As a rule, the cutaneous response is entirely different from that produced by the pharmacologic or toxicologic action of the drug.

4. Drugs with entirely different pharmacologic actions often produce identical eruptions; and the same drug is often capable of producing radically different manifestations in different individuals—or in the same individual at different times.

5. The amounts required to elicit eruptions are often much smaller than those necessary to produce pharmacologic or toxicologic effects.

6. Many drug eruptions occur only in certain predisposed individuals and, regardless of the deliberate increase in dosage, can never be made to appear in the majority of individuals.

7. The role of cumulative effects can usually be ruled out. As a general rule, drug eruptions can recur upon re-exposure to small amounts, even years after the last previous exposure . . . . and even when the last demonstrable vestiges of the previously administered drug have been eliminated.

8. The marked specificity of drug sensitivity can often be demonstrated. Individuals sensitive to one drug are frequently found to show no demonstrable sensitivity to isomers of that drug or to drugs with only slightly altered chemical constitution. But, just as has been demonstrated in sensitivity to living allergens, with drugs also, group specificity and cross reactions may be demonstrable.

9. The usual forms and the general phenomena found in other proven allergic . . . responses have their exact replicas in many recognized drug eruption. . . .

10. It has been shown experimentally that many of the substances producing drug eruptions are capable of sensitizing the skins of human beings and laboratory animals.

Drug eruptions are of various types ranging from simple erythema to the complex "fixed eruption". They may be produced by a variety of drugs (See list compiled by Sulzberger[178]). Convenient compilations of these eruptions are available[150]. The following data compiled by Sulzberger are to the point:

SOME COMMON DERMATOSES AND THEIR MOST FREQUENTLY CAUSAL DRUGS*

1. Acneiform, furunculoid and erysipelas-like eruptions—bromides, iodides, oils, tars.
2. Eczematous eruptions, with erythema, papulation, vesiculation, weeping and scaling—quinine, procaine, other local anesthetics, ephedrine, mercurials, formalin, sulfonamides, penicillin, arsphenamines, atabrine.
3. Erythema multiforme-like eruptions—phenolphthalein, antipyrine, salicylates, barbiturates, other soporifics, sulfonamides, penicillin, etc.
4. Erythema nodosum-like eruptions—iodides, bromides, salicylates, sulfonamides.
5. "Fixed eruptions," *i.e.*, fixed, circumscribed erythematous, edematous or bullous and polychromatic pigmented eruptions—phenolphthalein, antipyrine, phenacetin, barbiturates, salicylates, the arsphenamines, atabrine and other acridine and acriflavine derivatives, gold, sulfonamides (all so-called fixed eruptions have in common the *fixed*, circumscribed nature of the *site* of sensitivity and reaction, and thus all tend to recur *in situ*).

* Based on Sulzberger, M. B.: *Dermatologic Allergy* (Springfield, Ill.: Charles C Thomas, 1940[178]).

6. Lichenoid and lichen planus-like eruptions—arsenic, arsphenamines, atabrine and other acridine and acriflavine derivatives, gold, amphetamine sulfate (atopic dermatitis-like eruptions?).
7. Pemphigoid and ulcerating and vegetating eruptions—bromides, iodides, sulfonamides.
8. Purpuric eruptions—iodides, arsphenamines, particularly sulfarsphenamine, carbamides (sedormid), barbiturates, balsams, sulfonamides, etc.
9. Scaly eruptions, purely erythematous or scarlatiniform and morbilliform; dermatitis exfoliativa—arsenicals, atabrine, belladonna, balsams, heavy metals, nirvanol, salicylates, sulfonamides.
10. Urticaria and angioneurotic edema—salicylates, barbiturates, sulfonamides, penicillin, balladonna, atropine, iodides, bromides, the opium group, arsenicals, penicillin, phenolphthalein, amphetamine sulfate.

DERMATOLOGIC CONDITIONS WHICH MAY SHOW PARTICULAR SUSCEPTIBILITY TO REACTIONS TO PARTICULAR DRUGS*

1. Acne and acneform eruptions and furuncles are more susceptible** to iodides, bromides, androgens, other steroid hormones (and certain foods—chocolate, shellfish, and so on).
2. Atopic conditions are more susceptible to salicylates.
3. Dermatitis herpetiformis is more susceptible to iodides, bromides, thyroid products (and certain foods including shellfish, sea fish, chocolate, nuts).
4. Hypertrichosis is more susceptible to androgenic substances.
5. Moniliasis and moniliids are more susceptible to iodides and bromides.
6. Purpuric and hemorrhagic conditions are more susceptible to barbiturates, arsenicals, gold salts, sulfonamides and salicylates.
7. Recurrent herpes simplex is more susceptible to iodides, bromides, salicylates (and certain foods—chocolate, shellfish, caviar, nuts).
8. Seborrheic conditions, intertrigo, infected and impetiginized eczematoid eruptions are more susceptible to antisyphilitic arsenicals, gold salts, penicillin and sulfonamides.
9. Urticarial eruptions are more susceptible to salicylates, iodides, bromides and a great variety of other drugs and of foods.

* Sulzberger and Baer[178].

** More susceptible than a group of persons without these dermatologic changes or a history of these changes.

Specificity of Drug Reactions Cutaneous or Other. Although mention of specificity of drug reactions is made throughout this review, it might be emphasized here that the results of studies on the specificity of drug allergies are so variable that no generalizations are possible. Sherman[167] in his excellent review has presented the pertinent data on this matter as follows:

"This is best illustrated by sulfonamide sensitizations which have been most completely studied. Some patients sensitive to one sulfonamide drug have failed to react to any other members of the group. Other patients have reacted similarly to sulfadiazine, sulfathiazole and sulfapyridine but not to sulfanilamide. Still others have shown sensitivity to all drugs of the group. In some instances the sensitization was apparently to the para-aminophenyl radical and reactions were also obtained with sulfanilic acid, para-aminobenzoic acid and procaine. Park reported that 60 per cent of sulfonamide skin sensitizations were strictly specific for one drug while Sulzberger found only 10 per cent who failed to show cross reactions. Dowling, Hirsch and Lepper found that 69 per cent of sulfonamide sensitization reactions recurred if the same drug was used again but only 17 per cent if another drug of the group was substituted.

"In sensitizations to other types of drugs, instances of both strict specificity and group reactions have been reported. Cooke found that three aspirin-sensitive patients did not react to salicylic acid, benzoic acid, antipyrine, sodium acetate or methyl salicylate. Horsfall's patient, exquisitely sensitive to formaldehyde, did not react to other aldehydes, formic acid or methyl alcohol. Loveman reported a patient sensitive to alurate (allyl isopropyl barbituric acid) who did not react to barbituric acid or any of its other derivatives or to sedormid (allyl isopropylacetyl carbamide). On the other hand, Goodman described a case of a patient with procaine allergy who reacted to all the local anesthetics of the procaine group but not to those of the cocaine, quinoline or pyridine groups. Dawson and Gerbade reported a patient sensitive to quinine who reacted to seven related levorotatory compounds but not to quinidine, the dextroisomer

of quinine, or to any of the corresponding dextrorotatory compounds. Patients sensitive to arsphenamine usually react to all the related compounds containing trivalent arsenic but not to tryparsamide in which arsenic is pentavalent. However, there are several reports of arsphenamine sensitization in which the reactions to trial doses of tryparsamide have been the same as those to compounds of trivalent arsenic. In a given case of drug allergy only cautious trial will reveal whether other related drugs are tolerated."

Pathogenesis of Drug Eruptions. Eruptions and, or, other evidences of so-called idiosyncrasy to drugs have been an interest of physicians for many years, certainly as far back as the 18th century[1b,49]. In spite of this long concern and the present attention to this problem, the mechanism of drug eruption production is still obscure. In the past certain theories have been advanced to explain these eruptions. Among these are: "Saturation of the system" due to faulty elimination, particularly by the kidneys; "elective affinity" of certain drugs for anatomical elements, "irritation" of the skin due to the circulating drug, "modification of the sweat", chemical change of the drugs in the blood stream to products which led to certain eruptions, nerve origin; an endocrine stimulation with influences on the central and peripheral nervous system. The basis for our present understanding of the pathogenesis of drug eruptions was suggested only about 50 years ago when J. Jadassohn published his studies on idiosyncrasy as noted in drug eruptions. At present most writers[1b,43,49,111,167,168,174,177,187,201a,203a,b] believe that allergy is at the basis of most of these lesions. Other mechanisms for a smaller number of them are: cumulative effect (argyria); toxic effect (through liver?); non-allergic hypersusceptibility and biotropism (synergism). Sulzberger[177] has listed the following reasons for believing that drug eruptions are in general due to allergy.

1. Eruptions may be produced by *minute* amounts of drugs, sometimes long after the last medication—thus ruling out pharmacologic action and cumulative effect.
2. In most persons, regardless of large dosage, eruptions do not occur.
3. Eruptions usually recur from the *same* or *related* drug.
4. The clinical picture of a drug eruption is different from that due to pharmacologic action.
5. *Identical eruptions* may be produced by *unrelated* drugs.
6. One drug may produce different manifestations in different persons.
7. Some drugs may produce different manifestations in one person at different times.
8. Specificity of drug sensitivity can usually be demonstrated.
9. Some drugs, experimentally, sensitize skins of both humans and animals.
10. *Many manifestations that are produced by allergy to living microorganisms or to natural allergens can be reproduced by drugs:*

(a) Drugs, like other allergens, may exhibit incubation periods, spontaneous flare-ups and subsequent altered response to re-exposure.

(b) Can be ranged as to relative sensitizing capacity, *viz.*: non-pathogenic (cascara sagrada, yeasts, certain treponemes); facultative pathogens (phenolphthalein, monilia); obligatory pathogens (nirvanol, spirochaeta pallida, measles organism).

(c) Tend to produce characteristic pictures, *e.g.*: tubercle bacillus (tubercle); treponema pallidum (chancre); phenolphthalein (fixed eruption); arsphenamine (exfoliative dermatitis).

(d) Elicit variations in host susceptibility, *e.g.*: mouse (immune to syphilis); rabbits (immune to arsphenamine); all laboratory animals (immune to both gonorrhea and halogens).

(e) Produce changes which may persist for long periods.

(f) Exhibit spontaneous fluctuations.

(g) Are dependent upon environmental and dietary influences.

(h) Tend to select certain tissues and sites.

On the other hand, Dragstedt[49] believes there is substantial reason to conclude that a variety of drug idiosyncrasies may depend on various non-allergic factors, and it seems probable that some drugs may produce both

allergic and non-allergic types of toxic reactions at the same time. There is merit in attempting to distinguish between reactions, and to that end he suggests the following provisional criteria:

An allergic basis seems to be indicated, 1. When the pattern of the toxic reaction is consistent with that of the allergic disorders produced by antigenic agents. This means that reactions characterized by urticaria, cermatitis, angioneurotic edema and asthma are probably allergic in character; that reactions characterized by jaundice, acute yellow atrophy of the liver and optic atrophy are probably not allergic, while granulocytopenia, anemia, thrombocytopenia and polyneuritis may well be one or the other. 2. When a priming or sensitizing administration of the drug appears to be a factor in the history, while a non-allergic basis seems to be indicated when either long-continued administration or the use of substantial doses appears of major importance. 3. When the untoward reactions are alleviated by epinephrine, diphenhydramine hydrochloride ("benadryl hydrochloride" N.N.R.) and similar agents, whose ameliorating effects are most reasonably interpreted on the basis of an anti-allergic effect. A non-allergic basis seems to be indicated for those reactions which are alleviated by ascorbic acid, folic acid, thiamine and other agents whose ameliorating effect is not reasonably credited to an anti-allergic effect.

Immunology of Drug Eruptions. The immunologic mechanisms of drug eruptions, and drug allergy in general, has received considerable attention. On the whole, while there are data to support various viewpoints and beliefs regarding the mechanisms involved, final demonstration of the exact modus operandi of drug sensitivity is far from certain. For example, although Longcope[107] has apparently demonstrated the probable mechanism involved in serum sickness, a corresponding mechanism has not been demonstrated for the urticarial reactions to penicillin which are clinically identical with serum reactions. The development of antibodies and positive intracutaneous and other types of tests in these cases have been reported by some investigators and their existence denied by others[117]. At the Roosevelt Hospital Allergy Clinic in New York, Sherman[167] reports that neither the skin test nor passive transfer is a reliable index of penicillin sensitivity since small urticarial reactions to skin tests with penicillin may occur in non-sensitive individuals and the tests are often completely negative during or shortly after an urticarial reaction. Skin sensitizing antibodies were present in the serum of less than 10% of clinically sensitive patients and then in such low titres as to be of questionable significance. The antigen cannot be demonstrated in the circulating blood if the reaction occurs more than 24 hours after the last dose of penicillin even though there may be amounts of the drug adequate for antigenic activity still in the body during the reaction.

Although antibodies have been demonstrated to a few drugs (crystalloid non-protein substances), most of the persons with eruptions due to these products do not usually develop positive reactions to skin tests (intracutaneous) nor are antibodies demonstrable in the circulating blood. The usual methods of demonstrating antibodies do not seem to be of value in the case of drugs. Landsteiner's[95a,b] haptene theory has been invoked to explain this anomaly. He and others[36,96] suggest that slight local injury, sufficient to liberate tissue protein, may be caused by the drug. This protein assumes the character of an auxiliary antigen and can thus conjugate with the haptene "drug" forming a complete antigen. These protein drug conjugates have been demonstrated for certain drugs[155a]. However, when some of the protein conjugates[77,193] are used in experimental animals, the reaction is of the anaphylactoid type and does not resemble the effects of uncombined drugs in man. Sherman[167] and others

could not reproduce the high proportion of significant results obtained by Leftwich[99], who used sera of patients receiving adequate doses of the sulfonamides (which presumably contained sulfonamide bound to protein) as antigens for intracutaneous tests of sensitivity to corresponding drugs. A control test consisted of serum from the same patients when not receiving the drug.

Karsner and Hanzlik[83] thought that reactions to drugs were anaphylactoid changes induced by capillary thrombosis, agglutination emboli or capillary toxicity.

The relationship of drug allergy and infection in drug eruptions, especially after organic arsenical indication has been the special interest of Stokes and his co-workers[172d,174] for about 30 years. They conclude:

"1. The literature of the subject of arsphenamin dermatitis evidences a growing appreciation of the role of infections, local, focal and general, in the complex causal background of this condition.

2. A part of the influence of infection is probably exerted through the allergic mechanism of arsphenamin sensitization, and involves the conception of multiple balanced and summation effects, as suggested by Vaughan in general, by Harkavy and Hebald for infectious asthma and arthritis, and by the observations of Moore, Woo and Robinson on the reactivity of atopics to arsphenamin intradermally.

3. When the infection involves the skin, and also in antecedent or induced dermatitis from other causes, the local dermatitic focus acts as the excitant to a general flare-up following arsenical medication, through the vasodilation mechanism suggested by Auer, by Schlossberger and by Amalric.

4. Dermatophytic infections may apparently act as participants in a "balanced" or a "summation" allergic complex involving an arsenical extending the range and increasing the severity of the allergic dermatitic response to the drug (Block, trichophytin).

5. A dermatophytic focus may also conceivably serve, through the induction of local vasodilation, as the starting-point of an "arsenical" dermatitis.

6. Minute amounts of arsphenamin in arsphenamin-sensitive persons may flare up and tend to generalize a local, apparently mycotic dermatitis.

7. The interaction of a drug and infection allergy is, perhaps, reversible, and may in some cases take the course of Milian's "activation" of the infection focus, with an exanthem of the toxic erythema type and a flare-up of the local focus in the case of bacterial infections, or an exacerbation of the localized dermatomycotic process and a "mycotid" in the case of a fungus infection.

8. Clinical cases illustrative of these possibilities and of the interplay of multiple allergic susceptibilities and infection in the background of dermatitis (including the arsenical type) are presented. The last case described apparently combines explosive dermatitic response to an arsenical, to bismuth, to goose feathers, to a mycotic infection and to bacterial protein (Coley's serum) in observations extending over four years.

9. In dealing with arsphenamin dermatitis with focal infective lesions, mycotic or bacterial, treatment should be directed, albeit with caution, at the focal as well as the general process."

Diagnosis of Drug Eruptions. The diagnosis of drug eruptions frequently poses a challenge. The clinician often has an intuitive feeling that an eruption of local or widespread distribution is caused by a drug, though positive history of drug ingestion often may be lacking. The following clinical data and procedures have been employed with varying degrees of benefit in the definitive diagnosis of eruptions due to medicaments: 1, *Suggestive clinical picture* (outlined above); 2, *History*. The information that a patient is taking certain drugs may be of decided value in diagnosis if the following items are observed: initial exposure followed by a variable incubation period and then a sudden outbreak, increasing in severity and with a variety of constitutional symptoms, especially if the drug is continued, all point to the possibility of the eruption being of medicinal causation. But we must not forget that the ingestion or administration of the medicament and the

eruption may be coincidental; 3, *Course.* Improvement on withdrawal of the drug and flare-up after re-exposure. Readministration may be a hazardous procedure, even ending fatally. On the other hand, certain eruptions (*e.g.*, bromide, iodide) may develop slowly and disappear long after the drug has been withdrawn. Similarly, the eruption may not appear until years later (arsenical keratoses and carcinoma). There may be polyvalent sensitivity and the eruption may be due to the drug readministered; 4, *Diagnostic aids. a,* Cutaneous allergic tests are of little value. They may even be dangerous and induce sensitization (*e.g.*, arsenical intradermal tests[154], patch tests[13a,15b,c]), or severe reactions[71,191]. Furthermore the results may be falsely positive or negative. Passive transfer procedures are also unreliable; *b,* Chemical analysis of lesions, other tissues and body fluids may yield positive results, thus identifying the presence of a particular remedial agent, but the findings may be coincidental. Spectroscopic studies have the same limitations; *c,* *Histopathology.* This is certainly of value in the case of bromoderma and iododerma which produce a rather typical pathologic response (iodide or bromide granuloma). In other cases there may be no clue in the pathologic picture of drug versus other causation of the eruption (*e.g.*, lichen planus due to atabrine or arsenicals and lichen planus of iodiopathic causation). Recently Rich[152a,b] and other pathologists[59,102,125] have maintained that certain histopathologic changes occurring in experimental protein sensitization are characteristic of the allergic reaction, and have made the diagnosis of drug allergy on pathologic grounds in the absence of immunologic evidence. These changes consist of widespread foci of parenchymatous and collagenous degeneration with monocytic infiltration and arterial lesions resembling those of periarteritis nodosa and rheumatic fever. Similar lesions have been found in patients dying during or after sulfonamide therapy and occasionally other types of therapeutic agents, without receiving any foreign protein injections. Suggestive as the findings are, their use as conclusive proof of drug allergy in the absence of corroborative clinical and immunologic evidence has been challenged[92,162]; 5, *Blood.* Blood cell examinations are important, since blood dyscrasias often complicate a variety of drug eruptions.

We shall now detail certain aspects of the eruptions produced by a limited variety of medicaments. First among these is the characteristic eruption usually called "fixed".

Fixed Drug Eruptions. In 1894 Louis Brocq introduced the term fixed to indicate an eruption in which the cutaneous manifestations appeared as round or oval apparently edematous plaques from the size of a coin to that of a palm, recurring on various parts of the body and accompanied by an itching or burning sensation. The patches were dusty red at their onset and showed definite borders. At times these lesions progressed to form bullae. Desquamation or crusting (after the bullous lesions) appeared as the eruption faded, leaving a pigmentation of variable shade and duration in the areas affected. A special feature of the eruption was its tendency to relapse and recurrence of the lesions in the same sites.

The first drug from which such a process was noted was antipyrine. Soon after introduction of this drug in 1885 one type of eruption observed after its use was peculiar in that it recurred at the previously affected areas of the skin whenever antipyrine was again ingested. There were but few presentations on this subject until 1918, when Abramowitz[1a], who has done more than

any author to publicize and define the concept of fixed eruption, reported on 5 cases of erythema multiforme associated with cutaneous pigmentation. At about the same time Howard Fox[56] described an eruption which he took to be erythema perstans following ingestion of phenolphthalein. In 1922 Wise and Abramowitz[202] were able to determine that the changes in Abramowitz' original patients, as well as others subsequently observed, were in reality examples of phenolphthalein eruption. Since then a flood of papers on fixed eruptions has appeared. Among recent publications are those of Newman[133], Wise and Sulzberger[203a,b], Abramowitz[1a,d], Knowles, Decker and Kandle[93], Abramowitz and Noun[2], Belote and Whitney (list of phenolphthalein-containing preparations)[18], Abramowitz and Russo[3], Pillsbury (sensitivity to tryparsamide at sites of pigmentation from silver arsphenamine)[145], Chargin and Leifer (arsenicals)[35], Arnold, Jr.[8b], Dostrovski and Sagher (sulfonamides)[47], Freeman (sulfonamides)[58], Goldschlag (quiniline)[66], and Goodman and Arthur[67]. Much of the material in this discussion is from the works of Abramowitz and his colleagues.

In reference to drug eruptions, the term fixed does not indicate that such lesions are permanent or lasting since the eruption is not expected to reappear if the cause is eliminated. There are usually no permanent sequelae except from secondary or unrelated causes. The term fixed has been established by usage for such eruptions, even though they may never recur, because the reaction site is fixed and the eruption is observed to appear in the previously affected area or areas should a recurrence develop. Histologically these lesions present the features of banal dermatoses of the urticarial erythematous or eczematous varieties. In cases with pigmentation there are varying numbers of cells containing melanin in the subpapillary layer.

Many drugs are now known to be responsible for fixed eruptions. The following have been reported as having produced such lesions:

Acetanilid	Eucalyptus, oil of
Acetylsalicylic acid	Iodides
Acriflavine	Ipecac (emetine)
Aminopyrine	Ipomea
Antimony and potassium tartrate	Isacen
Antipyrine	Magnesium hydroxide (magnesia)
Arsenicals (acetylarsan, arsphenamines, mapharsen, trisodarsen, tryparsamide)	Mercury
Barbiturates	Phenolphthalein
Bismuth salts	Quinidine
Cinchophen	Quinine
Emetine	Salicylates
	Sulfanilamide and its derivatives

Although most of the drugs responsible are of the synthetic organic type, there is no relationship between them chemically which could account for their ability to produce such similar eruptions. Furthermore, there are reports that fixed eruptions have occurred in patients as a result of vaccines, liquors (alcoholic[131a,b]), Karaya gum[28], lentils[186], and tomatoes[42]. Wohlstein[205] has noted them after physical exertion and psychic stress, and Gougerot[68] found them resulting from certain metabolites. Menstrual disturbances have also been responsible for some cases[53]. Although a particular drug may be responsible for fixed eruptions in a grown patient, such lesions may occur independently. Thus Ehrmann[53] noted that at times one of his patients would develop an eruption from antipyrine whereas at other times it would occur without antipyrine medication. Wise[201b] had a patient who developed fixed lesions from phenolphthalein which reappeared after use of a barbiturate. Chargin's[34a] patient with fixed eruption from arsphenamine had a flare of the eruption after administration of phenolphthalein. Another patient reacted similarly to antipyrine and bismuth. In yet another[34b] a fixed

eruption produced by arsenicals flared up not only after arsenical but from use of phenolphthalein as well. Abramowitz and Russo[3] observed a patient with fixed lesions on the hands with a history that phenolphthalein, barbital and magnesium hydroxide, a good example of polyvalent specific sensitivity, manifested clinically as fixed eruption.

The mechanism of the production of fixed eruptions is as yet unknown. Certain facts bearing on this phase of the problem are worth mentioning. Tonnel and Raviart[184], as well as Mibelli[124], have indicated that antipyrine may be present in bullous type of fixed lesions induced by this compound. Local application (by rubbing) at the site previously affected with antipyrine ointment has reproduced a recurrence[7]. There is no definite information regarding the question as to whether other drugs may be found in fixed eruptions produced by them. Abramowitz[1d] has been unable to find either phenolphthalein or its conjugate in an eruption from that drug. Sandler[158] stated that he had demonstrated phenolphthalein in the normal skin of a patient with a phenolphthalein fixed eruption by means of the usual scratch test technique; but neither he[158] nor Abramowitz[1d] could subsequently confirm this. On the other hand, Lowenfish[112] believed he had detected, by a cataphoretic method, phenolphthalein in the skin of a patient with phenolphthalein eruption on the hands. He obtained negative results on one of Abramowitz' patients.

On the whole, after surface application, intracutaneous and subcutaneous injection, the various drugs responsible for fixed eruptions could not be recovered and identified. Bernstein[22], however, obtained positive patch tests with the offending drugs in the case of the eczematous type of eruption.

Transfer to normal subjects of sensitivity to phenolphthalein and other drugs producing fixed eruption has yielded variable results. Kenedy[87] reported success in transferring phenolphthalein sensitivity to 2 normal persons, but Abramowitz[1d] could not verify this claim by his own experiments using the same technique, namely, having the patients take phenolphthalein before they were given an intracutaneous injection of phenolphthalein before they were given an intracutaneous injection of phenolphthalein-sensitized serum (Walzer method). Rosenthal[155a] did obtain positive endermic reactions to phenolphthalein in patients apparently sensitized to phenolphthalein by the previous injection of homologous or heterologous serum containing conjugatid phenolphthalein. Jacobs and his co-workers[79] also were able to sensitize guinea pigs to phthalic-anhydride, one of the intermediates used in the preparation of phenolphthalein.

An interesting phase of this subject is the outcome of auto-transplants which indicate that the local hypersensitivity in these eruptions resides either in the epidermal layers or in the neurovascular structure of the cutis. Wise and Sulzberger[203a] transferred an affected area to a normal site and a normal area to the previously affected site. After complete healing, phenolphthalein was administered by mouth. Contrary to the results of Naegeli and his co-workers[130], as well as those of Urbach and his co-workers[188], Wise and Sulzberger[203a] found that the normal skin grafted on the previously affected area reacted in a typical manner with the production of a phenolphthalein lesion while the previously affected skin, now grafted on a heretofore normal site, remained unaffected. They interpreted this to indicate that the "shock site" of the sensitivity was dependent on the deeper structures (nerves and blood

vessels). Loveman[109], using similar technique in a patient sensitive to alurate, observed similar results. Knowles, Decker and Kandle[93] in identical experiments but which were repeated in 2 months, found the initial results to be similar to those of Naegeli and others[203a], but opposite to those of Loveman[109] and Wise and Sulzberger[203a]. However, 2 months later the results were in accord with those of the latter investigators. Knowles and his co-workers also concluded that the fundamental pathologic process involved is nervous or vascular. In their comprehensive study of fixed eruptions due to arsphenamines, Chargin and Leifer[35] performed auto-transplants in 3 patients. All of these full thickness auto-transplants failed to react when the particular drug was re-administered.

Fixed eruptions are not related to the nature of the agent nor are they toxic reactions to them. It is believed by Abramowitz[1d] that persons may be exposed for a period of time without ill effect and then the patient becomes sensitized. Although specific antibodies can be demonstrated only rarely, all the facts indicate to an allergic hypersensitivity underlying the development of the fixed eruption.

It is advisable at this point to re-emphasize the methods of determining the causative agent. Since cutaneous tests and even the demonstration of the suspected offending drug in certain body fluids or excretions do not yield conclusive causal relationship between the drug and the eruption, careful history is a very important part of the diagnostic machinery. Frequently the patient is unaware of drug ingestion, as, for example, in one of our patients[15a], when the phenolphthalein was administered in the form of effervescent salts which he received each time he came home intoxicated. His family was not aware that the salts contained phenolphthalein, although the can containing the salts warned that if the glass in which the salts were given was washed with soapy water, a red color would develop. The re-administration of the suspected drug may be dangerous and even fatal, so that in the last analysis, clinical diagnosis from the appearance of the lesions and their sequelae is safe and practical. The careful clinical observations in Abramowitz' original paper published in 1918[1a] should be consulted by anyone interested in this problem.

Atabrine Eruptions. One of the developments resulting from the mass use of a preparation in the recent war was the uncovering of a group of cutaneous reactions which have only recently been specifically attributed to atabrine. Although sporadic reports of atabrine dermatitis had previously been reported[135], this problem is clearly stated in the report of the Medical Consultants Division, Surgeon General's Office, U. S. Army[103a,b].

Atabrine is unquestionably valuable in the suppression of malaria. Untoward reactions attributable to the drug have been few, and in no instance have they been severe enough to warrant discontinuance of the drug in a military organization or in a geographic area. Usually, minor unpleasant reactions, such as intestinal disturbances, which occur early in the treatment, disappear in a few days when the drug is continued. In the latter part of 1943, however, medical officers in the Southwest Pacific Area called attention to a characteristic cutaneous syndrome occurring in soldiers evacuated from New Guinea and adjacent islands. Lieut. Colonel Charles Schmitt and Major Thomas Nisbet, dermatologists stationed with general hospitals in that area, were the first to report the disease and its probable etiology. Later similar cases were reported from all

other theaters where suppressive atabrine medication was in general use as a control measure for malaria. This cutaneous syndrome, "atypical lichen planus", may exhibit: "violaceous and erythematous hypertrophic lichenoid papules and plaques, frequently with a rough verrucous surface; violaceous and erythematous, oozing or scaling eczematoid plaques well demarcated in some cases and ill defined in others; flat, squamous, geographic plaques on trunk, axillae, and groins similar to tineal lesions; white, sometimes violaceous-tinged, slightly elevated mucous membrane lesions identical with those seen in typical lichen planus; oozing intertriginous dermatitis in the groins, axillae, and posterior surface of the ears; ecthymatous lesions; scaling and superficial fissuring of the lips; and scaling erythematous eczematoid dermatitis of the eyelids. In some cases, the lesions are predominantly lichenoid; in others, most of the plaques are eczematoid. Almost all patients have both violaceous, hypertrophic lichenoid plaques and some form of cutaneous eczematoid reaction. During the course of the disease, a considerable number of these patients have acute, explosive generalized exacerbations, manifested by oozing eczematoid dermatitis having a predilection for the flexors, groins, axillae, extremities, and neck. Such exacerbations resemble exfoliative dermatitis and a few of these patients may develop a secondary exfoliative dermatitis which is as severe as the cases of primary exfoliative dermatitis described below. The seriousness of such a state and the need for expert management of these patients cannot be overemphasized"[103]. The details of the etiologic, clinical and therapeutic aspects of this complex are given in Livingood and Desaude's report[103].

In summary these authors made the following general statements regarding atabrine and reactions attributable to atabrine:

"1. The military value of atabrine in suppressing *vivax* malaria and curing *falciparum* malaria far outweighs untoward effects which have been attributed with reason to the use of the drug.

"2. Suppressive doses of atabrine greater than 0.7 gm. per week should not be employed routinely. This amount has been shown to provide adequate protection against clinical attacks of malaria, provided 'atabrine discipline' is strictly enforced. In clinical treatment of malarial attacks with atabrine, routine dosage should not exceed 2.8 gm. in seven days.

"3. Atabrine suppressive medication should be discontinued promptly and atabrine should not be given for clinical treatment when individuals develop the following conditions: atypical lichen planus, unexplained chronic eczematoid dermatoses, unexplained toxic erythematous eruptions, exfoliative dermatitis, severe leukopenia, agranulocytosis, and aplastic anemia, acute hepatitis (not including disturbances believed to be due to malaria), or toxic psychoses which can be reasonably attributed to atabrine after careful clinical study.

"4. It should be remembered that drugs other than atabrine, such as the sulfonamides and arsenicals, may be harmful in individuals with the conditions mentioned above.

"5. Caution should be exercised in attributing disease conditions to atabrine until careful and complete studies have been made over a period of time to establish such relationship. Because of the widespread use of atabrine, its administration inevitably coincides with many diseases with which the drug has no connection. Even if a connection is established between atabrine and a given untoward effect, its significance relative to the military value of atabrine requires evaluation. Since the use of atabrine became widespread, clinical attacks of *falciparum* malaria have been almost eliminated and deaths from malaria have been extremely rare. There is no question of the general superiority of atabrine over quinine, both for suppression and for clinical treatment."

Numerous other papers have appeared detailing certain aspects of the atabrine problem. We mention some of these briefly. In 1945 Sulzberger and Baer[178] give an illustrated statement of this syndrome in their article on skin tests. Whitehall[196], and Nelson[132] have each reported individual

cases of this process. Kierland[88a] analyzed his experience with 29 cases. Atabrine dermatitis and an associated aplastic anemia were reported by Drake and Moon[50]. Rosenthal[155b] made a study of the histopathology of atypical lichen planus. His material comprised 21 specimens from all phases of the process. Goldberg[65] described the unusual features of this dermatosis. Two cases of vesicular eczematoid type of drug eruption from atabrine were reported by Becker[14]. Bereston[20] analyzed observations on 200 cases of lichen and dermatitis. Lutterloh and Shallenberger[113] collected 8 cases of unusual pigmentation at uncommon sites presumably due to atabrine. Ochronosis-like pigmentation was observed by Sugar and Waddell[176]. A case of fatal exfoliative dermatitis and hepatitis was encountered by Agress[4]; Ginsberg and Shallenberger[54], as well as Kierland and his associates[90], noted fluorescence of nails of persons taking atabrine. Pfaff[143], and Nisbet[134], described the dermatologic aspects of dermatitis due to atabrine. Hyperkeratosis of the palms and soles due to this drug was reported by Paxton[138]. Cases of atypical lichenoid or atypical lichen planus were renewed by Alden and Frank[5], by Holbrook[76], and by Singh[170], Bazemore *et al.*[12], Wilson[200a], and Waddell[190]. In a well documented discussion, Benedek[19b] attempted to prove that "Atypical Lichen Planus" was really a cutaneous manifestation of Vitamin A deficiency. In 1949 Schmitt[160], one of the early students of the problem, reported on the present status of Quinacrine (atabrine) dermatitis. It is of interest that veterans have residual lesions and recurrences of eczematoid dermatitis which they acquired in the tropical areas during, or after the recent war. Affected individuals are increased risks in any occupation requiring exposure to heat, friction or chemicals.

Sulfonamides. While the sulfonamides have been a boon to the successful combatting of infections, the medical and lay public learned soon after their introduction into the practice of medicine that they were two-edged swords. These drugs are capable of interfering with the life and activity of bacteria and some viruses and at the same time they have potential toxic and allergic by-effects on nearly every organ of the host. While the cutaneous reactions are, of themselves, relatively less serious than those which involve the hematopoietic system (agranulocytosis, hemolytic anemia) and kidneys (obstruction by crystals), the cutaneous manifestations serve to remind the practitioner of more serious consequences which may be on the way or are actually present in subclinical form. While the exact number of fatalities from the sulfonamides is unknown, 200 such cases have been reported[106].The proportion of fatal cases that are solely cutaneous is also unknown but in a report of fatal sulfonamide exfoliative dermatitis by Weinstein and Domm[195] autopsy failed to reveal any satisfactory cause of death. Furthermore, in the report on sulfonamide toxicity as a cause of death in New York City in 1941[179], among 28 probable sulfonamide deaths, 3 cases of dermatitis in all probability died of the cutaneous involvement, 2 of these had generalized dermatitis which followed sulfathiazole therapy, and the 3rd succeeded upon the administration of sulfapyridine.

The literature on sulfonamide cutaneous reactions has been extensively reviewed. Bloom's paper[25] should be read in its entirety by the interested reader. Greenwood[70] classified the cutaneous reactions resulting from sulfonamides into 3 categories: 1, Direct toxic effects from overdosage or cumulative effects. Subsequent administration of small doses in such patients

after recovery may not lead to recurrence. 2, Purely allergic reactions: in such cases an incubation period, usually 7 days between the first and second dose, is required for the sensitization to become manifest. 3, Allergotoxic. In some cases it is possible that the earliest manifestations of the toxic type of eruption was a faint finely papular exanthem. On continuation of the drug there was spread of the eruption and it became scarlatiniform, morbilliform or maculopapular. No lymphadenopathy accompanies it. Allergic dermatitic symptoms appear early in the course of sulfonamide administration and usually are characterized by itching, sneezing, lachrymation, and dyspnea with edema of the lips, eyelids and face. These eruptions may be of various types (see below). Allergotoxic eruptions usually appear after 7 to 14 days of average dosage.

Light sensitivity after administration of sulfonamides was noted early in the sulfonamide period. We have discussed this phase briefly in our review on Light Sensitivity[172c]. This phenomenon is not necessarily associated with sensitivity to the drug, although in some cases there may be limitation of the dermatitis to the areas exposed to the sun[37]. According to Combes and Canizares[40], however, sensitivity to sunrays is not common following sulfanilamide administration.

The constant sunshine of the Middle East and the presence of a considerable number of ambulant patients with venereal disease undergoing chemotherapy in an open-air hospital, recently gave R. G. Park and W. M. Platts (N.Z.M.C.)[137] unusual opportunities to observe cases of the light-sensitive type of sulfonamide dermatitis. During the 12 months from October, 1940, to September, 1941, 486 patients received sulfanilamide, of whom 21 developed eruptions (4.3%); 309 received sulfapyridine, with 6 cases of eruptions (1.9%). Of the 27 cases, 8 occurred during July, and 6 during August. As measured by the photo-electric cell, the intensity of visible light in this part of the Middle East in July is about 4 times that in January. Photosensitivity occurred from the 8th to the 10th day of administration. Two patients were found to be photosensitive 2 days after chemotherapy was stopped. It appears that patients given sulfonamides for more than 6 days are possible victims of sunlight eruptions. The commonest lesions are erythematous papules in a morbilliform or roseoliform pattern, becoming confluent. Itching varies from severe to slight and is absent in some cases. Less common lesions are edema, urticaria, vesiculation, pustulation and desquamation. Fever and malaise were present in 12 patients. Most rashes subsided in 2 to 4 days. In many cases the presence of melanin is a protection against sun eruptions. Three observations support this view: 1, about one-third of patients are subjects who sunburn easily; 2, the bronzed parts of the body tend to be affected less than the others; 3, no eruptions have ever been seen in Maoris, who comprised about 100 of the patients treated during the 12 months. The following parts are affected in order of severity: 1, parts exposed to the sun during chemotherapy; 2, parts exposed in the past; 3, pressure points, such as the great trochanters; and 4, least of all, parts always kept covered, such as the bathing-trunk area. Avoiding exposure to sunlight, 6 patients completed their course of chemotherapy, and 3 had further courses later without ill effects. In the milder cases, a rash is no indication for discontinuing the drug.

More recently Watkinson and Hillis[192] observed transient eruptions in 136 (34.6%) of 470 men at an R.A.F.

station who were given a 10 day course of sulfanilamide, 2 gm. daily, as prophylaxis for streptococcic infections. Most of the men were vaccinated against smallpox shortly before, during or after sulfanilamide administration, and appearance of the eruption coincided in all instances with development of the vaccination pustule. The role of photosensitization was indicated by the occurrence of lesions exclusively in areas exposed to light—head and neck, except for a small V-shaped area on the forehead shaded by the forage cap, arms and forearms unprotected by sleeves, and, in a few cases, a small band about the ankles. A few men who had been sunbathing had more extensive rashes. In most instances the lesions were erythematous macules or maculopapules, although in 4 cases vesiculation was observed. The rash faded within 1 week, leaving brown desquamating areas. In 23 cases the eruption was confluent and associated with conjunctivitis, fever and malaise, simulating measles. The 136 affected men were divided into 4 groups, on the basis of time of vaccination with relation to administration of the sulfonamide. The men in the 1st group, in whom vaccination pustules developed while the drug was being given, showed the highest incidence of eruptions (49.8%). Those in the 2nd group, in whom vaccination pustules developed 8 days after sulfanilamide therapy was discontinued, also showed a surprisingly high incidence of cutaneous reactions (26.3%). In the 3rd group of men, in whom vaccination reactions had subsided, 4 eruptions (4.6%) were noted. These occurred only in patients with unhealed vaccinations. No rashes were present in the 4th group of 71 men, in whom vaccination was not performed or was unsuccessful.

In none of the cases did the rash recur on further exposure to sunlight. Patch tests were negative in 30 cases, indicating that the eruption was a transient photosensitivity rather than a true sulfonamide dermatitis. Possibly, the vaccination pustule acted as an inflammatory focus from which toxins were liberated by the sulfonamide, causing photosensitivity.

We have noted the production of light sensitivity following virus infection (*cf.* lymphogranuloma venereum[171] with and without ingestion of sulfonamides. This occurs often in the so-called virus pyogen sequence[172d]).

Many types of eruption may follow the use of sulfonamides. Among them are morbilliform[161,185]; scarlatiniform erythema multiforme[44]; erythema nodosum[105]; urticarial and angioneurotic edema[15]; purpura, varioliform[57], vesicular[182]; bullous[54a,69,84b,104,135,165,175,185]; pustular; follicular; fixed eruption[39,47,58,110,123]; psoriasiform[144]; exfoliative dermatitis[81,129,179195]; pemphigus foliaceous-like eruption[197], and bacterids[33].

Most of these processes differ little from similar eruptions produced as a result of administration of other drugs. There are, however, certain features of some of them which deserve special mention. At the outset, it should be noted that any type of eruption may result from any of the sulfonamides, and once a patient has developed a reaction to one preparation it is unsafe to administer another. For example, Arnold[8a] pointed out that it is not safe to administer succinylsulfathiazole to patients known to be sensitive to sulfathiazole. Sometimes, however, one type may be responsible for the majority of cases of a particular eruption. Most of the erythema nodosum-like eruptions have followed the use of sulfathiazole, but it has occurred after sulfanilamide or sulfadiazine. Löfgren in this connection stated that in his 24 cases of this type of eruption, the provocation effect of sulfathiazole was established, it was probable with re-

gard to sulfanilamide and possible but not demonstrated with regard to other sulfonamides. The bullous eruptions are frequently serious and even fatal. They may in all respects resemble those produced by phenolphthalein. Benedek[119a] believes that cutaneous eruptions due to sulfonamides were of 2 forms from the standpoint of mechanism of production: 1, genuine drug eruption, and, 2, Milian's biotropic effect. The former was of morbilliform or bullous type, the latter was pompholyx in type.

The relative incidence of cutaneous reactions produced by the sulfonamides may vary from preparation to preparation and even different lots of the same preparation, more of the various sulfonamides may be considered entirely safe in this regard. The literature gives highly variable figures and at best they do not represent the actual incidence since statistics dealing with individuals receiving repeated courses of sulfonamides yield considerably higher figures. For example, Lyons and Balberor[114] observed 53 patients (17 control and 36 patients) who had tolerated the first course of sulfathiazole (4 gm. followed by 1 gm. every 4 hours during a period on an average of 5 4/5 days); 19 (36%) developed severe fever reaction during the second course of the drug therapy given 2 to 20 days later. Note should be made that if a patient does react during early therapy, the result is usually mild but subsequent reaction is apt to be severe or less fatal. The cutaneous reaction may be associated with other serious by-effects, especially in the hematopoietic system. The route of administration for development of sensitization may be only by injection or even local administration for therapy or testing for sulfonamide hypersensitivity[104,165,175]. Note was made above regarding the question whether ingestion of one sulfonamide sensitizes the patient to other sulfonamides. While the evidence on this point is not entirely clear nor very imposing, the trend is toward the occurrence of cross sensitization.

With these features in mind, the incidence of sulfonamide reaction may be better appreciated. Dowling and Lepper[48] noted among their 500 patients treated with sulfonamides the following incidence of dermatitis; fever and, or, conjunctivitis 2.4%; from sulfadiazine 2%. Long, summarizing the literature[106], noted 5.2% of eruptions after sulfathiazole therapy; 2.2% after sulfanilamide, 2% following sulfapyridine and 1.3 from sulfadiazine. Park and Platts[137] found the incidence of eruptions following sulfanilamide to be 4.3%, but only 1.9% after sulfapyidine. Other estimates from various compounds range from a total of 3.7 to about 10%.

The presence of sulfonamides in tissues may be determined by a histochemical method developed by MacKee, Herrmann, Baer and Sulzberger[115a,b]. Full details are given in the original communications. It employs Ehrlich's Reagent (p-dimethylaminobenzaldehyde) and has proved satisfactory in numerous studies in the cutaneous penetration of sulfonamides, after their solution in penetrating vehicles and their external application to grossly intact human and animal skins.

The pathologic changes produced by sulfonamide allergy in man have been studied extensively. More and his colleagues[125] found that the lesions usually combined necrosis of the tissues with activity of the reticulo-endothelial system. The findings suggested that the lesions were always an expression of allergy. French[59] noted striking histopathologic changes in 76 autopsies and 2 additional specimens of skin taken for biopsy from patients apparently sensitized to sulfonamides. Char-

acteristic acidophilic histiocytes were present in focal and diffuse infiltrations in 17 organs. Significant vascular lesions were characterized by fibrinoid necrosis, endothelial edema, and proliferation. Lichtenstein and Fox[102] observed a patient with necrotizing arterial lesions resembling those of periarteritis nodosa and focal visceral necrosis following the administration of sulfathiazole. Although no specific pathologic picture of the cutaneous lesions was recorded, it is worthy of note that the fatal reaction in this case began with a vesicular eruption. Geeves[62] emphasizes the danger signal afforded by cutaneous lesions. In his 3 fatal cases of streptococcal infections coming to autopsy, 2 with generalized purpuric eruption showed severe fatty metamorphosis of the liver and moderate fibrinoid necrosis of the liver and mesenteric lymphnodes. In the third case without skin lesions there were no splenic nor lymphatic findings.

Keefer[86] has summarized the problem of sulfonamide eruptions as follows:

"Skin Reactions.—Among the common untoward reactions to the sulfonamides are various skin eruptions. They are characterized by their pleomorphism, and are frequently accompanied by other signs of drugs intoxication or hypersensitivity. They vary in frequency with different drugs, and they are often widespread in distribution. The lesions cannot be inhibited by the administration of para-aminobenzoic acid. There is nothing distinctive about the eruptions, since they may be erythematous, morbilliform, urticarial or purpuric, and in some cases a generalized exfoliative dermatitis, with massive edema, appears. Lesions resembling erythema nodosum are most frequently seen following sulfathiazole therapy. One of the curious features of some of the cases of dermatitis, especially those following sulfanilamide, is the fact that the eruption develops after exposure to sunlight, or, at least, is made worse following such exposure.

"The skin eruptions occur at one of three periods following the administration of the drugs. The usual time is between seven and nine days after the drug is started, although the lesions may appear as early as the fourth day. They may occur, however, as a prompt or accelerated reaction within 24 hours after the drug has been started, or as late as 2 to 6 weeks. When the skin eruptions are prompt or accelerated, they almost invariably occur in persons who have previously received the same or a closely related drug. For example, the usual story is that they received the same or a different sulfonamide at some time in the past, and that a reaction consequently followed within 7 to 14 days. This delayed reaction, which was self-limited in duration, disappeared following withdrawal of the drug. Then, after an interval varying from a few days to months or even several years, the same drug or a different one is given, with a prompt reaction. The prompt reactions may occur after single small doses, and they may be more extensive and serious than the previous reactions, since they are sometimes associated with exfoliative dermatitis or the signs of toxic hepatitis. Although these prompt or accelerated reactions occur oftener in patients who have had reactions following the first experience with the drug, they may appear in those who have previously had the drug without any noticeable reactions. Patients who have acquired sensitivity to sulfa-pyridine may react in a similar manner to sulfamethylthiazole of sulfapyridine, but not to sulfanilamide, and patients who are sensitive to the esters of para-aminobenzoic acid (procaine hydrochloride) may be sensitive to sulfanilamide (para-aminobenzoic sulfonamide). It is plain, then, that the hypersensitivity to the drug may be specific, and that the reactions may follow the exhibition of a closely related drug. This suggests that there is a common substance in the various drugs to which some patients become sensitive.

"In most cases, the prompt hypersensitive skin eruptions are accompanied by fever, and in some, they may be associated with such features as toxic hepatitis.

"Delayed skin eruptions . . . occur commonly between the 7th and 9th day after the drug is started, and fever is associated with the eruption in about half the cases. The fever may subside within 2 to 7 days after the drug is withdrawn, but the skin eruptions may persist for several weeks or even longer. Other associated features are generalized edema, enlargement of the lymph nodes, leukocytosis (often reaching a count of 70,000 or 80,000), transient jaundice without anemia, and eosinophilia (20 to 55%). The delayed skin eruptions may also be a feature in the patients with neutropenia or in the cases of jaundice occurring as late as

the 6th week after the drug has been discontinued.

"Although many observers have not encountered serious reaction to the sulfonamides and others have advocated long continued oral administration (*e.g.*, 2 weeks after completion of treatment[181a,b] to prevent sensitization to these drugs the dermatologists of New York[46] found it necessary to adopt the following resolution:

'Whereas, Repeated administration of sulfonamides either internally or locally may sensitize an individual to these drugs and thereby preclude their future use in serious diseases, such as pneumonia; therefore, be it

'Resolved, That the Section on Dermatology and Syphilology go on record as strongly disapproving the indiscriminate use of sulfonamide drugs in relatively harmless diseases of the skin which can be satisfactorily treated by equally efficient drugs; and be it further

'Resolved, That the Section condemn the use of prepared dressing containing sulfonamide drugs which are sold promiscuously to the laity.'"

Penicillin. The literature on Penicillin reactions is already colossal. Fortunately Ethan Allan Brown[29] has performed a great task by reviewing this subject for the period 1943-48. This review is based on 308 papers and an additional 52 papers, in which sensitivity is mentioned, but neither defined nor described, published from March, 1943, to October, 1948. The reader is referred to this paper for the references to the reports cited here. The earliest report indicating cutaneous reaction was that of Keefer and his colleagues who found 14 instances of urticaria among their 500 patients. Lyons claimed urticaria as the commonest single complication occurring in 5.7% of 209 surgical cases (U. S. Army). He classified his patients into 2 groups: those who reacted to a particular batch with chills, headache, facial flushing, muscular cramps, nausea, vomiting, and those who reacted to any type of penicillin with fever, urticaria and transient azotemia. Duemling in 1946 summarized the results of treatment in 17,879 Naval patients treated with penicillin for 65 clinical conditions. Of these, 892 were patients with latent, early and neurosyphilis. Of the total group 10% sustained Herxheimer reactions, urticaria, pruritus and fever. Thomas (1948) in an experience of 10,000 cases, found urticaria to lead the list in respect to frequency of reaction type (2.5%). This occurred in 7 to 12 days after onset of therapy, and persisted 4 to 5 days regardless of the continuation or discontinuance of penicillin therapy. Usually the penicillin would be continued after onset of urticaria. Angioneurotic edema occurred after penicillin oil beeswax (2 cases in 804 treated). Erythematous papular and dermatitic reaction occurred in a number of patients. Bullous dermatitis occurred in 2 patients. Cormia and his co-workers encountered 0.5% reactions among 2000 soldiers given prolonged penicillin treatment. Urticaria and angioneurotic edema were among the reactions listed. They observed a syndrome resembling serum sickness, acute syncope with transient urticaria-like eruptions, erythematovesicular eruptions, dermatophytid-like reactions and erythema nodosum. Intradermal tests with 3 brands of penicillin gave partial results in 84, 65 and 23%, respectively. Some patients with severe reactions gave negative results. Among 116 control subjects there were also some positive reactions. Crystalline penicillin also caused some of the reactions. Numerous other reports showed a variable incidence of cutaneous reaction to penicillin, of various types and routes of administration. Peck and his associates found that among those who had had no previous penicillin, reactions occurred in 5%, but among those who had received previous treatment, the incidence rose to 25%. Males sustained more reactions than females. Skin tests (intradermal) were positive in variable percentage. There is a variety of types of cutaneous reactions.

Among those resulting from oral and parenteral injection are:

ORAL ROUTE:

Stomatitis and glossitis.
Melanoglossia (black tongue) (lozenges).
Aphthous stomatitis.
Thrush.
Glossodynia and exfoliation of filaments of filiform papillae of tongue.
Varicelliform eruption.
Urticaria and angioneurotic edema.
Dermatitis.

LOCAL CONTACT WITH SKIN. Not discussed here, but contact sensitization may occur after previous oral administration.

INJECTION. *Urticaria:* May occur shortly or days after injections are started or some time after treatment is concluded. (acute or delayed reaction). The intervals between treatment courses may be of importance. Urticaria may be due to concomitant treatment (*e.g.*, penicillin and heparin). Urticaria is often sole reaction to penicillin but may be associated with other signs and symptoms of serum sickness. Reactions may be serious enough to cause discontinuance of therapy.

Local Reaction: Induration and sterile abscess at site of injection of penicillin in beeswax reported by various authors. Cellulitis or pseudocellulitis have also been noted.

Pruritus without rash.
Morbilliform eruption.
Bullous eruption.
Purpura.

Exfoliative Dermatitis: These may be severe. Patient may be sensitized by contact and react by injection. Exfoliative dermatitis may be delayed reaction.

Dermatophytosis-like reactions.
Activation of dermatophytic focus.
"Id" reaction.

The most careful studies done by Cormia and Lewis elicited the relationships between sensitization to penicillin and pre-existing fungus disease. Following a series of 8 experiments, the authors concluded that many of the local and systemic reactions occurring during or after penicillin therapy were the result of a previous sensitization by a dermathophyte. In 45 children, aged 2 months to 6 years, who had never previously demonstrated fungus disease or received penicillin therapy, there was a nonspecific immediate reaction after intradermal tests with 1000 units of penicillin, with no delayed 48 hour reactions. In 17 patients, however, who presented active fungus disease, but had received no penicillin, immediate reactions occurred following intradermal tests with 41% of the subjects, developing the 48 hour tuberculin type of reaction. Of 8 guinea pigs, 5 developed papular lesions following the 2nd intradermal injection of penicillin given 28 days following the initial injection. In these 5 animals, the injection sites of the positive reactions were not flared up by intravenous injection of penicillin. There was no anaphylactic shock. Four of the 5 animals gave positive reactions to intradermal trichophytin injections. Five guinea pigs given weekly intradermal injections of trichophytin for 4 injections, followed a week later by intradermal injections of penicillin, did not develop sensitivities to either trichophytin or penicillin. A trichophyton gypseum infection induced in 6 guinea pigs resulted in positive intradermal reactions to penicillin in 3. In 7 rabbits with trichophyton purpureum infection of the skin, 5 developed positive reactions to penicillin.

In a later paper, Cormia, Lewis and Hopper evaluated the relationship between sensitization to penicillin and sensitization induced by superficial fungus disease by the Schultz-Dale test, using guinea pigs infected with T. gypseum or sensitized to penicillin. They demonstrated that in guinea pigs, anaphylactic sensitization to commercial sodium penicillin might be induced by a single injection given intradermally, or to crystalline penicillin sodium by a single intradermal, or 4 daily, intraperitoneal, injections. The guinea pigs could be sensitized anaphylactically to crystalline penicillin, in guinea pigs infected with T. gypseum. The authors feel that this positive reaction confirms the supposition that there is a common antigen in penicillin and the pathogenic fungi, which causes superficial fungus disease and that shock-like reactions in man are due to pre-existing sensitization by such pathogenic fungi.

Aggravation of bacterids.

Sensitization to penicillin may occur with different lots of the drug. Desensitization may be successful, according to Peck and associates, and O'Donovan and Klorfajn. A variety of drugs have been advocated in the treatment of penicillin cutaneous reactions. Intravenous nicotinic acid in doses of 35 mg. in 10 cc. of distilled water has been reported by Service for control of urticaria. The antihistaminic drugs, epinephrine, and similar preparations, have been used with variable results (Willcox, Pillsbury, *et al.*). Para-aminobenzoic acid has also been found of

value (Kampmeier; Gelfand). Procaine intravenously (1 gm. in 500 cc. of isotonic saline given in 2 hours) has been used by Van Root for urticaria. Vitamin K, Vitamin B and various other more specific measures have been used in therapy of these reactions.

Brown summarizes this subject as follows:

"At the present time information concerning penicillin reactions may be summarized as follows: 'The reactions occur most frequently in patients who have had several courses of penicillin. The continuation of penicillin treatment of a patient who has reacted with urticaria may or may not be tolerated. Skin tests are unreliable in predicting the occurrence of reactions and the anti-histaminic drugs may or may not control the reactions and permit continuation of penicillin therapy.' Pillsbury and his associates state that the urticaria reactions may be persistant and severe and may be accompanied by asthma and may be followed by ecchymoses and uterine bleeding. It is their opinion that the incidence of urticarial reactions is increasing as suggested by the fact that 1.8% of reactions occurred in the first 824 cases of syphilis treated at the University of Pennsylvania, whereas 12 cases have occurred in the last 200 patients treated between October 1945, and May 1946. Of 23 cases of urticaria treated with antihistaminic drugs, 16 with Benadryl were relieved in 14; with no relief in 2 and 7 treated with PBZ showed relief in 2 and none in 5. In their opinion, penicillin must be halted as soon as a reaction occurs, unless there is immediate critical need of the drug. Antihistaminic agents should be given by mouth 3 times daily or slow intravenous injection in isotonic saline is advised if the reaction is severe. After subsidence of the urticaria or the accompanying symptoms, a test dose of another brand of penicillin (1,000 U.) may be given, while the antihistaminic drug is continued by mouth. If there is no reaction in 6 hours, a second dose of 10,000-20,000 U. can be used followed by the full therapeutic dose if there is no reaction within 4 hours. The antihistaminic drugs should be continued and gradually reduced over a period of 2 to 3 days. No compounds prolonging the serum level of penicillin should be used during the period of trial administration. If re-administration is impossible and therapy is desirable, cautious administration should be resumed after an interval of 4 or more weeks."

The available literature on streptomycin suggests that the same types and factors in drug sensitivity are being observed after use of this drug.

Arsenicals. The problem of arsenicals of various types producing cutaneous reactions has been covered in a vast literature. We have reviewed several aspects of arsenical eruptions in this Journal on two occasions. In our review of The Trivalent Arsenicals in Syphilis[172a,b] the types of eruptions and certain factors in their pathogenesis were discussed. In the review on Tumors of the Skin[15d,e] the arsenical keratoses and cancer were covered. In the present compilation we shall, therefor, mention some of the loose ends not touched upon in the previous presentation. Furthermore, the introduction of penicillin into syphilotherapy has materially lessened the incidence of these cutaneous reactions.

Arsenical jaundice has been given considerable attention lately. Most of the current literature has been reviewed, in connection with his own experience, by Ambrose King[91]. He concludes that the common prevalent type of post-arsphenamine jaundice is probably due to an infective agent introduced in the course of injections. It is preventable by careful technique in the sterilization of syringes and in the preparation of fluids for injection. The less common form of post-arsphenamine jaundice is possibly a sensitization phenomenon and due to individual idiosyncrasy. There is no known method of prevention, although some established cases may benefit from sulphur-containing amino-acids in adequate dosage. Subsequent arsenical therapy may be entirely well tolerated, but usually those in the group in which sensitization is suspected may require preliminary desensitization.

The 9th day erythema of Milian is usually regarded as harmless and is not an indication for cessation of arsenical therapy. Leifer[99], however, has called attention to the danger of continued arsenotherapy in these cases of erythema of the 9th day. In a series of 14 instances of characteristic reaction continuation of arsenical after the initial reaction led to serious parenchymatous damage in the form of jaundice, agranulocytosis, with or without nephritis. It is interesting to note that 12 of the 14 patients subsequently tolerated penicillin therapy without incident.

Barbiturates. The literature on barbiturate reaction is voluminous. This is largely due to the numerous preparations belonging to this class of medicaments and to the alertness of the physician to the cutaneous manifestations produced by these drugs. A sample of recent literature affords ample illustration of the variety of cutaneous eruption as well as the demonstration that many types of barbiturate are responsible for them. Occasionally, however, one type of drug may lead to an excessive number of a particular reactions, *e.g.*, Purpura hemorrhagica[122]; from sedormid[75,78*]. The same hemorrhagic cutaneous reaction may occur from phenobarbital in therapeutic doses (in a patient with myocardial infarction[200a]). Severe exfoliative dermatitis is occasionally encountered after these drugs. It may eventuate in recovery[127], or fatally[164].

In general, the more frequently observed types of reaction to the barbiturates include a sensitization reaction, manifested chiefly by urticaria, pruritus and a toxic type such as morbilliform or scarlatiniform maculopapular erythema which in severe cases may lead to severe bullous (even hemorrhagic) process. Fixed drug eruptions are also occasionally observed[109]. Loveman pointed out in this connection that cutaneous sensitivity to one barbiturate does not preclude sensitivity to other members of the group. Light sensitivity induced by the barbiturates is discussed in our review on Photodynamic Effects in Dermatology[172c]. Occasionally a granulomatous lesion may occur[140] and recently Berlin[21] has observed ectodermosis erosiva pluriorificialis due to phenobarbital. The observation that barbiturate given to the lactating mother may appear in human milk[120] has suggestive implications for the infant.

Bromides and Iodides. An interesting and controversial chapter in the problem of drug eruptions is that of the halogens (bromides and iodides). In spite of the obvious relationship of certain clinically specific cutaneous processes to iodide or bromide ingestion or administration, publicity of these usually occasional reactions has played a somewhat deterrent role in the universal consumption of goiter-preventing iodized salt. Although there is usually agreement that these preparations do produce eruptions or aggravate certain existing cutaneous processes, the point of departure is in assessing the magnitude of the problem. However, recently Gaul and Underwood[61] have presented evidence suggesting that iodized salt does not unfavorably affect the course of acne vulgaris, a finding reminiscent of Sutton's[180b] proposal to use iodized salt in the therapy of this disease. Without attempting to resolve the various viewpoints in this controversy, we present some of the recent reports of cutaneous reactions in patients receiving these halogens. The severe non-cutaneous reactions sometimes occurring with the cutaneous will not be detailed.

Bechet[13b] has covered the etiologic role of iodized table salt in iododerma and incidentally he has collected the available literature on many aspects of the iodide problem. He came to the

* Incorrectly classed with the barbiturates since sedormid is allyl-isopropyl-acetyl-carbamide, a hypnotic. (H. B.)

following conclusions, dramatically opposite to those cited above:

Since 1924, iodized salt has been recommended indiscriminately to the public, which has been assured of its complete safety. As a result, it is being used by thousands as a tonic, without even the knowledge that it is useful in goiter, and in ignorance of the fact that severe iododermas and even death, have followed the administration of iodine in less than medicinal doses, among its users.

Fifteen deaths are cited from the literature, and 3 non-fatal cases of iododermas of the bullous type, seen during the past year alone in patients using iodized salt are briefly described for the first time.

The role of iodized salt in the etiology of acne in many patients is well recognized by dermatologists. Its relationship to the acneform iododermas has been proved by the fact that the lesions disappear on its elimination only, or with the administration of ordinary salt. Recurrences on again taking iodized salt have occurred. Its etiologic relationship is some cases of acne vulgaris is shown by failure of response to roentgenotherapy until its use is discontinued. On questioning such patients, a history of the ingestion of iodized salt for long periods, was elicited, and they showed no improvement with roentgenotherapy. *All improved rapidly after discontinuing iodized salt, and the administration of sodium chloride by mouth or intravenously.* Acneform iododermas occurred in 18 cases, and the results from Roentgen-ray therapy were equally unsatisfactory *until the iodized salt was stopped and sodium chloride given.*

In a recent report Ehrich and Seifter[52] described a fatal case of thrombotic thrombopenic purpura resultant from kelpidine, a commercial reducing agent containing kelp and iodine. These investigators suggest that the purpura was caused by an antigen antibody reaction involving cells of the thrombocytic series. The involved cells agglutinated or disintegrated and occluded many capillaries; as a result the blood was depleted of thrombocytes and thrombopenic purpura ensued. Purpura following iodine therapy is rarely observed and the specific type described by Ehrich and Seifter is unique.

Eruptions From Miscellaneous Drugs. *Chloral Hydrate.* It is possible to to find a person sensitive to practically every drug. For this reason it would be a futile task to list all the reports dealing with individual examples of reactions to this or that preparation. However, we shall mention certain recent reports. Baer and Sulzberger[10] have observed an instance of eczematous dermatitis due to chloral hydrate following both oral and topical application. This is a significant finding since dermatologists and others are prone to consider chloral hydrate a safe and satisfactory sedative especially for patients suffering from barbiturate or bromide eruptions. The distribution of the reaction in Baer and Sulzberger's case resembled that of hematogenous eruptions following the use of the sulfonamides (scalp, face, neck, hands and forearms).

Liver Extract. The parenteral administration of liver extract has been reported infrequently. Jones[82] was able to collect 16 reports of reactions in the Quarterly Index Medicus to 1939. Only 6 of these were in the American literature. The reported reactions include mainly skin and pulmonary manifestations. Urticaria was the most frequently recorded cutaneous type. One patient with erythema nodosum was in this series. Jones, personally, had 2 patients with allergic reactions to this preparation, one exhibiting urticaria and the other anaphylactoid phe-

nomena. The sensitivity to liver is said to disappear after a time and desensitization is reported as possible. Administration of liver internally is also possible. We have observed one patient who developed urticaria only after liver extract of hog origin. Beef liver preparations were innocuous. The reactions in this case occurred after either parenteral or oral use of the preparations.

Trimethadione (Tridione). This preparation, recently introduced for the therapy of petit mal and related disorders, has been found to produce certain toxic phenomena among which are cutaneous lesions. Acneform lesions have resulted on occasion following its use. Shaffer and Morris[166] have reported severe erythema multiforme of the pluriorificial type (Stevens-Johnson Syndrome) resulting in blindness in a white boy aged 6½. Among other treatment he had received trimethadione in dosage of 0.3 gm. twice a day for about 16 days. (During this period 6 doses of 0.5 to 1 cc. of polyvalent anterior pituitary extract were also administered.) Three days before the last dosages of trimethadione were taken a red spot developed at the site on the buttock of an injection of the pituitary extract. However, on this date another injection of this product in the other buttock did not lead to a local lesion at this site. The following day bullae had developed about the lips. On the day following the last trimethadione injection a generalized eruption accompanied by fever, severe cough and dyspnea resembling asthma had appeared. During a stormy course the process subsided but not without permanent damage to the eyes. Tests (including passive transfer) with pituitary extract and trimethadione gave negative results. Although there is strong suggestion that trimethadione was the offending substance in this case, there is no clear-cut proof of this, since simultaneous administration of more than one preparation confounds the issue. Recently Leard and his co-workers[97] have reported on a patient with hepatitis, exfoliative dermatitis and abnormal bone marrow occurring during tridione therapy.

Mesantoin. Methylphenylethyl hydantoin (Mesantoin), which has proved to be useful as an anticonvulsant in epilepsy, may cause serious side effects, among which are reactions of the skin and changes in the blood. Although the eruptions are usually benign and respond quickly to cessation of treatment with the drug, it is possible for this complication to be of a serious nature.

Ruskin[157] has recently reported the results of one year's administration of methylphenylethyl hydantoin to a group of 26 institutionalized patients. He indicated that 1, the occurrence of toxic reactions did not necessarily increase proportionately with the dosage; 2, toxic reactions appeared to depend more on the patient than on the drug. Of the toxic reactions, the complaint of drowsiness was the most frequent, but was independent of the dosage or the concurrent administration of phenobarbital. Only 1 patient (3.8%) presented an eruption. This was scarlatiniform in nature and appeared when the patient received only 0.1 gm. daily. The lesions disappeared when treatment with the drug was discontinued and did not reappear when the patient was again receiving the drug. By starting, the second time, with a smaller dosage and raising the dosage slowly, it was eventually possible for the patient to receive 0.3 gm. daily.

Since the completion of the 1 year study of the original 26 patients, the drug has become more plentiful and more patients are gradually being added to the original group. In only one of these did a rash develop. Unfortunately, this bullous eruption did

not present the fairly innocuous picture the writer might have expected from his own past experience or the experience of others. The author, therefore, warns against the unbridled enthusiasm which often follows the development of a new fairly successful treatment for a condition which, in the past, has been so unresponsive.

Hydantal (5-phenyl-5-ethyl-3-methylhydantoin) another anticonvulsant for use in epilepsy produces eruptions in about 4.5% of cases in which it is administered in combination with phenobarbital[150]. The eruption usually appears within 2 weeks and may disappear within about 10 days when treatment with the drug is discontinued.

Dilantin Sodium (Phenytoin; sodium diphenyl hydantoinate). By now the hypertrophy of the gums produced by this anticonvulsant is well known. In addition this preparation may produce a variety of cutaneous reactions. For example, Finkelman and Arieff[55] found one patient with a scarlatiniform eruption with fever and 6 with "pruritus" as well as 17 cases of gingival hyperplasia among their 41 patients treated with phenytoin sodium according to the method of Merritt and Putnam.

Nirvanol Eruptions. Nirvanol (phenylethyl hydantoin), a preparation for treatment of chorea, known to the Europeans since 1916 and introduced to American physicians in 1930 by Ray and Cunningham[151], always produces cutaneous symptoms accompanied by a definite symptom complex after it has been administered for a certain fixed time and in exact amounts. Madden[116] in 1932 made an extensive review of the literature on this drug and as a result of his personal experience found the symptoms to appear with clock-like precision. On the second or third day after the administration of nirvanol is begun, the choreic movements are greatly exaggerated. They are soon followed by sedative effects. Fever generally develops from the 7th to the 9th day, reaches a maximum in 24 hours and subsides during the next day or so. If the drug is continued, the fever is prolonged. The eruption usually appears between the 9th and 12th days. The lesions appear at first on the covered parts of the body and appear on the face and in the more severe cases. It is usually morbilliform and may resemble one of the cicate exanthemata. Stomatitis, bullous or ulcerative, has also been described. It is of short duration but may recur. The histopathology of the lesions is the same as found in any toxic erythema. The prognosis of nirvanol eruption is usually good.

Dinitrophenol. Although one rarely has occasion nowadays to use dinitrophenol in the therapy of obesity, this preparation was extremely troublesome more than a decade ago. Beinhauer[17], for example, recorded the case of a patient who had developed urticaria following its use. Hitch and Schwartz[74] in 1936 observed a patient who had developed multiple and severe reactions including exfoliative dermatitis, cataracts and polyneuritis. In his comprehensive study, Simkins[169] noted that "skin rashes, which are common, no longer excite their quondam fear." Because development of cataracts is too high a price to pay for weight reduction, Simkins felt that the clinical use of dinitrophenol should be reserved for urgent indications only.

Acetophenetidin. Often regarded as dangerous, this drug has been championed recently by Cohen[38] who concluded that there is little or no evidence to justify the inclusion of this compound in the category of dangerous drugs. He does, however, include it in the list of some of the drugs which cause dermatoses (allergic). There is no specific type of eruption caused by acetophenetidin. The types of cuta-

neous manifestations noted in this review include exanthemata, urticaria (angioneurotic edema), flushing of the face, and petechiae.

Mercurials. The subject of mercurial eruptions has been reviewed thoroughly by Wright[206] and Billo[23]. These findings need not be repeated here, but the report of Gibbs, Shank and Pond[63] on the absorption of externally applied ammoniated mercury is a reminder of the frequently overlooked possibility of widespread eruption and other mercurial lesions resulting from the local application of this medicament.

Bismuth Compounds. The cutaneous reactions to bismuth compounds have been fully covered in Modern Clinical Syphilology[173]. While penicillin therapy has largely eliminated this complication from bismuth, the introduction of new bismuth preparations for oral use in various dermatoses leaves a possible fruitful source for such reactions. Bismuth pigmentation is still reported[194].

Antihistaminic Drugs. The various antihistaminic drugs (such as Benadryl and Pyribenzamine) have as yet yielded but little cutaneous reaction. Although an occasional case of dermatitis medicamentosa occurs from their use, they are singularly infrequent[54b,c, 72,101,149]. The possible occurrence of granulocytopenia from one or another of these preparations[24] suggests necessary vigilance for cutaneous and other reactions. Rives and his colleagues[153a] have just reported a fatality from ingestion of Thenylene (Methapyrilene).

Various Drugs. A number of drugs have on occasion recently been reported as productive of eruptions. For example, alopecia has been noted following the use of the antispasmodic cyverine hydrochloride[100]; exfoliative dermatitis from diethylstilbesterol[84a]; eczematous eruption from Carter's Little Liver Pills (Podophyllin)[41]; toxic erythema and exfoliative dermatitis resulting from the administration of sulfocyanates in the treatment of hypertension[11]; erythematous and morbilliform and purpuric eruptions due to ephedrine[9]; scarlatiniform eruption[159]; and exfoliative dermatitis[128] from codeine[162]; argyria has been fully discussed in the monograph by Hill and Pillsbury[73]. Recently Boersma and Baker[26] in a study of the distribution of silver deposits in a patient with argyria, observed that the membrane propsia of the large axillary sweat glands contained little silver in contrast to the dense concentrations of silver in the connective tissue surrounding the small sweat glands. This disposition of silver seemed to be directly related to the difference in concentration of elastic tissue in the connective tissues enveloping the two types of glands. The revival of interest in gold products because of their effectiveness in arthritis has led to an ever growing literature on the reactions to gold compounds. While there have been numerous reactions in other systems, the cutaneous phenomena have been summarized by Kierland[88b] as follows: Cutaneous reactions are many, varying from simple evanescent erythema and pruritus to protracted universal exfoliative dermatitis or erythroderma. Urticaria or erythema multiforme may be the sole evidence of toxicity, while pruritus, localized or generalized, alone may be the symptom. Morbilliform and scarlatiniform eruptions are seen which may subside promptly when use of the drug is discontinued or may progress to exfoliative dermatitis. Rarely, eruptions simulating those of pityriasis rosea and lichen planus may be seen. Metallic gold may be deposited in the skin and give rise to a condition known as chrysiasis or auriasis. This is manifested by a diffuse slate-colored darkening of the skin and usually appears late in the course

of treatment or even months after treatment with gold has been discontinued. Thiouracil eruptions have been evaluated by the Council on Pharmacy and Chemistry of the American Medical Association[189]. Among 5745 patients in the report, 189 (3.3%) presented the following eruptions: urticaria 64; papular rash 37; morbilliform rash 23; erythema 18; macular rash 17; acneiform rash 3; pruritus 3; edema of legs 1; and unspecified dermatitis 23. It should be pointed out that these cutaneous reactions to thiouracil were usually mild, but the occurrence of urticaria in such high proportion cannot be summarily dismissed (*cf.* sulfonamides). These reactions were independent of dosage.

Chloroquine [7-chloro-4 (4-diethylamino-1-methylbutylamino)]. Quinoline, an antimalarial drug produced lichen planus-like eruptions in 2 individuals[6]. In spite of the increased and widespread use of amphetamine sulphate (benzedrine) and its analogue dextroamphetamine sulphate (dexedrine) only 1 questionable case of dermatitis was found by Kauvar, Henschel and Ravin[85] after a thorough search of the literature. They described an additional case of their own from amphetamine sulphate. Patch and scratch tests with the drug yielded negative results.

Aspirin (acetyl salicylic acid). Increasing numbers of fatal reactions to this universally used preparation are appearing, but in proportion to the number of people exposed to this medicament the incidence of reactions is indeed small[51,60,94]. Most of the reactions are thought to be of an allergic nature. Urticaria and purpura are the most frequent cutaneous reactions. Angioneurotic edema comprised 19% of the patients with reactions in Prickman and Buchstein's[147] series of hypersensitization to aspirin.

Treatment. Withdrawing the offending drug is usually effective of cure of drug eruption in a reasonably short time. However, because of certain exceptions, notably the halogens (bromide and iodide) and the arsenicals, auxiliary methods of treatment are required. No attempt will be made to outline all the procedures, but some of the recent proposals in this connection will be mentioned briefly.

Although penicillin may not be the last word in syphilotherapy, it has removed the much feared cutaneous reactions incident to the arsenical treatment of this disease. Prior to the introduction of penicillin a number of procedures for reaction prevention were detailed by Stokes and Beerman[172a,b] and by Stokes, Beerman and Ingraham[173]. Among the substances mentioned were sugars, calcium salts, degradation products of protein including the amino acids and other materials for admixture with the arsphenamine solution. No conclusion had been reached as to their actual merit. Vitamin C has been studied particularly; we (Beerman, Pariser and Wammock[16]) believe that derivative of this vitamin may have merit at least in the less severe cases. Sodium thiosulfate is no longer considered potent and clinical syphilologists have discarded it in the past 10 years. Liver extract has also enjoyed a certain amount of more or less deserved popularity not only for reactions to the arsenicals but for reactions to other preparations such as the sulfonamides. Pelner[139] believes that the action of whole liver extract in ameliorating the toxic effects of sulfonamides and diethylsilbesterol is through its high content of ascorbic acid. Nicotinamide, Vitamin K, thyroid extract and certain hygienic measures have also been employed.

"BAL." Despite the advances made in controlling arsenical reactions, the therapeutic and preventive armamentarium was at best only partially effec-

tive. As a by-product of successful intensive search for a substance that would serve as an antidote to the arsenical gases, it was found that 2, 3 -dimercaptopropanol (BAL; British anti-Lewisite), discovered by Peters and his British co-workers[141] in 1945, was also effective in the therapy of certain metal intoxications. The literature on this remarkable substance has grown to large proportions since security regulations regarding it were removed. The July 1946 issue of the Journal of Clinical Investigation was devoted entirely to various studies on BAL. Randall and Seeler[148] in 1948 compiled all the published material available to the time of their review. Since these sources are readily available we shall mention only those facts pertinent to the question of prevention and treatment of drug reactions. Although BAL has afforded some additional ideas as to the mechanism of heavy metal action, it has not clarified the modus operandi of drug eruptions. Furthermore, BAL is not entirely innocuous either from the local or the sensitization standpoints. In specific poisoning by metals, BAL has been found effective or of suggestive value in those caused by arsenic, mercury, gold, lead, cadmium, silver and certain miscellaneous metals: antimony, tellurium, copper, chromium, nickel, zinc, thallium, selenium and vanadium. Further study is necessary to determine the precise value of BAL in the case of many of the latter elements. Since BAL may increase the toxicity of certain metals, it should not be used indiscriminately. BAL is commercially available in a preparation containing peanut oil and benzyl benzoate which is suitable for intramuscular injection only.

In the eruptions due to arsenic, especially the organic arsenicals (arsphenamines, arsenoxides), BAL has proven itself to be of exceptional value both in essential recovery as well as relief of symptoms. In severe cases, edema, fever and pruritus disappear or greatly decrease in 24 hours and complete recovery takes place within 2 weeks. However, some patients respond only partially and require additional courses of BAL. Some cases may completely fail to respond. Development of abscesses at the sites of injection are fairly frequent. Although others have demonstrated the efficacy of BAL in other complications of arsenotherapy, we cite as a typical experience the results of Carleton, Peters and Thompson[32]. They used BAL in 44 cases of arsenical dermatitis; 41 of these patients had the acute exfoliative type. Three cases ended fatally and in 4 more it was impossible to measure the progress numerically. In the remaining 37 cases the mean number of days between the first injection of BAL and healing or nearly complete healing was 21.5 days. Eight cases developed abscesses at the site of injection.

It was hoped that the antihistaminic drugs would be effective against drug reactions of the skin, but not only are they of limited value, but as previously stated, dermatitis may occur as a result of their administration.

Since Wile and others[198,199] used sodium chloride in the therapy of iodide or bromide eruptions several other procedures have been proposed in the treatment of these eruptions. Wohl and Robertson[204] found the desoxy-corticosterone acetate in conjunction with sodium chloride was effective in bromide intoxication (noncutaneous). Bondurant and Campbell[27] had previously found that adrenal cortex when given in combination with sodium chloride was apparently of value in the excretion of bromide and bromide effects. They presumed that the adrenal cortex restores the normal physiologic level of chloride.

Martin, Fisher and Thompson[118] found that the acute toxicities of sulfanilamide, sulfathiozole and sulfapyridine were markedly reduced (without diminution of therapeutic effect) by the prophylactic use of physiologic detoxifying agents such as cysteine, amino-acetic acid, calcium glucuronate and ascorbic acid. McGinty and his co-workers[121] found that nicotinic acid also relieved sulfanilamide reactions. This was advised on the basis of the similarity of certain aspects of sulfanilamide reactions to pellagra and radiation sickness. They began treatment with 50 mg. 3 times a day on the 4th day of sulfonamide administration.

REFERENCES

(1.) **Abramowitz, E. W.**: (a) Arch. Derm. and Syph., **31**, 777, 1935; J. Cut. Dis., **36**, 11, 1918; (b) New York State J. Med., **37**, 128, 1937; (c) Med. Clin. N. Am., 1323, September 1938; (d) Arch. Derm. and Syph., **43**, 672, 1941. (2.) **Abramowitz, E. W.**, and **Noun, M. H.**: Arch. Derm. and Syph., **35**, 875, 937. (3.) **Abramowitz, E. W.**, and **Russo, J. J.**: Ibid., **41**, 707, 1940. (4.) **Agress, C. M.**: J. Am. Med. Assn., **131**, 14, 1946. (5.) **Alden, H. S.**, and **Frank, L. J.**: Arch. Derm. and Syph., **56**, 13, 1947. (6.) **Alving, A. S., Eichelberger, L., Craige, B., Jr., Jones, R., Jr., Whorton, C. M.**, and **Pullman, T. N.**: J. Clin. Invest., **27**, 60, 1948. (7.) **Apolant, H.**: Derm. Zeit., **6**, 67, 1899. (8.) **Arnold, H. L., Jr.**: (a) Staff Med. Clinic, **13**, 138, 1947; (b) Staff Med. Clinic, **14**, 9, 1948. (9.) **Ayres, S., Jr.**, and **Anderson, N. P.**: J. Am. Med. Assn., **97**, 437, 1931.

(10.) **Baer, R. L.**, and **Sulzberger, M. B.**: J. Allergy, **9**, 519, 1938. (11.) **Baker, T. W.**, and **Brunsting, L. A.**: J. Am. Med. Assn., **108**, 549, 1937. (12.) **Bazemore, M., Johnson, H. H., Swanson, E. R.**, and **Hayman, J. M.**: Arch. Derm. and Syph., **54**, 308, 1946. (13.) **Bechet, P. E.**: (a) New York State J. Med., **39**, 829, 1939; (b) J. Invest. Derm., **8**, 409, 1947. (14.) **Becker, F. T.**: Arch. Derm. and Syph., **54**, 338, 1946. (15.) **Beerman, H.**: (a) Arch. Derm. and Syph., **28**, 758, 1933; (b) Ibid., **28**, 296, 1933; (c) Penna. Med. J., **39**, 690, 1936; (d) Am. J. Med. Sci., **211**, 480, 1946; (e) Ibid., **212**, 479, 1946. (16.) **Beerman, H., Pariser, H.**, and **Wammock, V. S.**: Am. J. Syph., Gon. and Ven. Dis., **27**, 58, 1943. (17.) **Beinhauer, L.**: West Va. Med. J., **30**, 466, 1934. (18.) **Belote, G. H.**, and **Whitney, H. A. K.**: Arch. Derm. and Syph., **36**, 279, 1937. (19.) **Benedek, T.**: (a) Urol. and Cut. Rev., **50**, 89, 1946; (b) Ibid., **51**, 267, 1947. (20.) **Bereston, E. S.**: J. Invest. Derm., **7**, 69, 1946. (21.) **Berlin, C.**: Arch. Derm. and Syph., **56**, 771, 1947. (22.) **Bernstein, F.**: Derm. Zeit., **62**, 368, 1931. (23.) **Billo, O. E.**: Am. J. Med. Sci., **201**, 756, 1941. (24.) **Blanton, W. B.**, and **Owens, M. E. B., Jr.**: J. Am. Med. Assn., **134**, 454, 1947. (25.) **Bloom, D.**: N. Y. State J. Med., **43**, 1499, 1943. (26.) **Boersma, D.**, and **Baker, B. L.**: Arch. Derm. and Syph., **57**, 1009, 1948. (27.) **Bondurant, C. P.**, and **Campbell, C.**: J. Am. Med. Assn., **116**, 100, 1941. (28.) **Bowen, R.**: Arch. Derm. and Syph., **39**, 506, 1939. (29.) **Brown, E. A.**: Ann. Allergy, **6**, 723, 1948. (30.) **Brunsting, L. A.**: Minn. Med., **24**, 169, 1941. (31.) **Burgess, J. F.**: Canad. Med. Assn. J., **51**, 25, 1944.

(32.) **Carleton, A. B., Peters, R. R.**, and **Thompson, R. H. S.**: Quart. J. Med., **17**, 49, 1948. (33.) **Carpenter, C. C.**, and **Gorsuch, P. L.**: U. S. Naval Med. Bull., **44**, 681, 1945. (34.) **Chargin, L.**: (a) Arch. Derm. and Syph., **37**, 144, 1938; (b) Ibid., **38**, 474, 1938. (35.) **Chargin, L.**, and **Leifer, W.**: J. Invest. Derm., **3**, 443, 1940. (36.) **Chase, M. W.**: Proc. Soc. Exp. Biol. and Med., **59**, 134, 1945. (37.) **Clark, T. W.**: J. Am. Med. Assn., **123**, 958, 1943. (38.) **Cohen, A.**: Acetophenetidin, privately printed. (39.) **Cole, L. M.**: Arch. Derm. and Syph., **54**, 675, 1946. (40.) **Combes, F. C.**, and **Canizares, O.**: Arch. Derm. and Syph., **44**, 236, 1941. (41.) **Conroy, J. A.**: J. Am. Med. Assn., **118**, 1449, 1942. (42.) **Cooke**, cited by Abramowitz and Russo[3].

(43.) **Dammin, G. J.**, and **Bukantz, S. C.**: J. Am. Med. Assn., **139**, 358, 1949. (44.) **Dardinski, V. J.**: Am. J. Clin. Path., **15**, 28, 1945. (45.) **Dennie, C. C.**: J. Am. Med. Assn., 120, 197, 1942. (46.) Dermatologists of New York: New York State J. Med., 1497, 1943. (47.) **Dostrovski, A.**, and **Sagher, F.**: Arch. Derm. and Syph., **49**, 418, 1944. (48.) **Dowling, H. F.**, and **Lepper, M. H.**: J. Am. Med. Assn., **121**, 1190, 1943. (49.) **Dragstedt, C. A.**: J. Am. Med. Assn., **135**, 133, 1947. (50.) **Drake, J. R.**, and **Moon, H. D.**: Calif. Med., **65**, 154, 1946.

(51.) Editorial: Is Aspirin a Dangerous Drug? J. Am. Med. Assn., **124**, 777, 1944. (52.) **Ehrich, W. E.**, and **Seifter, J.**: Arch. Path., **47**, 446, 1949. (53.) **Ehrmann, S.**: Die Anti-

pyrinexantheme, in Mracek, F.: Handb. d. Hautkrankh, 4th ed., Vienna, A. Hölder, **1**, 654, 1902. (**54.**) **Epstein, E.:** (a) Arch. Derm. and Syph., **41**, 61, 1940; (b) J. Am. Med. Assn., **134**, 782, 1947; (c) J. Invest. Derm., **12**, 151, 1949.

(**55.**) **Finkelman, I.,** and **Arieff, A. J.:** J. Am. Med. Assn., **118**, 1209, 1942. (**56.**) **Fox, H.:** J. Cut. Dis., **36**, 252, 1918. (**57.**) **Franks, A. G.,** and **Traub, E. F.:** Arch. Derm. and Syph., **46**, 737, 1942. (**58.**) **Freeman, H. E.:** Ibid., **50**, 45, 1944. (**59.**) **French, A. J.:** Am. J. Path., **22**, 679, 1946.

(**60.**) **Gardner, E.,** and **Blanton, W. B.:** Am. J. Med. Sci., **200**, 390, 1940. (**61.**) **Gaul, L. E.,** and **Underwood, G. B.:** Arch. Derm. and Syph., **58**, 439, 1948. (**62.**) **Geeves, E. F.:** Am. J. Med. Sci., **207**, 331, 1944. (**63.**) **Giggs, O. S., Shank, R., Pond, H.,** and **Hansmann:** Arch. Derm. and Syph., **44**, 862, 1941. (**64.**) **Ginsberg, J. E.,** and **Shallenberger, P. L.:** J. Am. Med. Assn., **131**, 808, 1946. (**65.**) **Goldberg, L. C.:** Ibid., **130**, 775, 1946. (**66.**) **Goldschlag, F.:** Med. J. Australia, **2**, 501, 1942. (**67.**) **Goodman, M. H.,** and **Arthur, R. D.:** Arch. Derm. and Syph., **43**, 692, 1941. (**68.**) **Gougerot, H.:** J. Med. franç., **19**, 160, 1930. (**69.**) **Greenberg, S. T.,** and **Messer, A. L.:** J. Am. Med. Assn., **122**, 944, 1943. (**70.**) **Greenwood, A. M.:** New England J. Med., **224**, 237, 1941.

(**71.**) **Hansen Pruss, O. C.:** Ann. Allergy, **7**, 219, 1949. (**72.**) **Harris, M. C.,** and **Shure, N.:** J. Allergy, **18**, 408, 1947. (**73.**) **Hill, W. R.,** and **Pillsbury, D. M.:** Argynia. The Pharmacology of Silver, Baltimore, Williams & Wilkins, 1939. (**74.**) **Hitch, J. M.,** and **Schwartz, W. F.:** J. Am. Med. Assn., **106**, 2130, 1936. (**75.**) **Hoffman, A. M., Kalm, J.,** and **Fitzgibbon, J. P.:** Ibid., **110**, 725, 1938. (**76.**) **Holbrook, A. A.:** Am. J. Med., **4**, 525, 1948. (**77.**) **Horsfal, F. L., Jr.:** J. Immunol., **27**, 553, 1934. (**78.**) **Huber, H. H.:** J. Am. Med. Assn., **113**, 674, 1939.

(**79.**) **Jacobs, J. L., Golden, T. S.,** and **Kelley, J. J.:** Proc. Soc. Exp. Biol. and Med., **43**, 74, 1940. (**80.**) **Jadassohn, J.:** A Contribution to the Study of Dermatoses Produced by Drugs. Selected Essays and Monographs. New Sydenham Soc., London, **170**, 205, 1900. (**81.**) **Johnson, R. D.:** J. Am. Med. Assn., **124**, 979, 1944. (**82.**) **Jones, C. A.:** Internat'l. Clinics, **3**, 259, 1939.

(**83.**) **Karsner** and **Hanzlik,** quoted by Wells, G. The Chemical Aspects of Immunity, Chem. Cat. Co., 1925. (**84.**) **Kasselberg, L. A.:** (a) J. Am. Med. Assn., **120**, 117, 1942; (b) Ibid., **123**, 1035, 1943. (**85.**) **Kauvar, S. S., Henschel, E. J.,** and **Ravin, A.:** Ibid., **122**, 1073, 1943. (**86.**) **Keefer, C. S.:** (a) Med. Clin. N. Am., **23**, **1133**, **1939**; (b) New England J. Med., **226**, 266, 1942. (**87.**) **Kenedy, D.:** Gior. ital. d idermat. e sif., **75**, 965, 1934. (**88.**) **Kierland, R. R.:** (a) Proc. Staff Meet. Mayo Clin., **21**, 404, 1946; (b) Am. Pract., **2**, 750, 1948. (**89.**) **Kierland, R. R.,** and **Brunsting, L. A.:** Ibid., **17**, 28, 1942. (**90.**) **Kierland, R. R., Sheard, C., Mason, H. L.,** and **Lobitz, W. C.:** J. Am. Med. Assn., **131**, 809, 1946. (**91.**) **King, A.:** London Hosp. Gaz., No. 1, 50: Clin. Suppl., 1947. (**92.**) **Klemperer, P.:** Pathologic and Anatomic Aspects of Allergy, In Robert A. Cooke, Allergy in Theory and Practice, Philadelphia, W. B. Saunders, 1947. (**93.**) **Knowles, F. C., Decker, H. B.,** and **Kandle, R. P.:** Arch. Derm. and Syph., **33**, 227, 1936. (**94.**) **Krasnoff, S. O.,** and **Bernstein, M.:** J. Am. Med. Assn., **135**, 712, 1947.

(**95.**) **Landsteiner, K.:** (a) The Specificity of the Serological Reactions, Springfield, Ill., Charles C Thomas, 1936; (b) New Eng. J. Med., **215**, 1 & 199, 1936. (**96.**) **Landsteiner, K.,** and **Chase, M. W.:** Proc. Soc. Exp. Biol. and Med., **49**, 688, 1942. (**97.**) **Leard, S. E., Greer, W. E. R.,** and **Kaufman, I. C.:** New England J. Med., **240**, 962, 1949. (**98**) **Leftwich, W. B.:** Bull. Johns Hopkins Hosp., **74**, 26, 1944. (**99.**) **Leifer, W.:** Am. J. Med. Sci., **210**, 458, 1945. (**100.**) **Levin, O. L.,** and **Behrman, H. T.:** J. Am. Med. Assn., **118**, 41, 1942. (**101.**) **Levin, L., Kelly, J. F.,** and **Schwartz, E.:** New York State J. Med., **48**, 1474, 1948. (**102.**) **Lichtenstein, L.,** and **Fox, L. J.:** Am. J. Path., **22**, 665, 1946. (**103.**) **Livingood, C. S.,** and **Desaude, F. R.:** (a) Bull. U. S. Army Med. Dept., **4**, **653**, **1945**; (b) J. Am. Med. Assn., **129**, 1091, 1945. (**104.**) **Livingood, C. S.,** and **Pillsbury, D. M.:** Ibid., **121**, 406, 1943. (**105.**) **Löfgren, S.:** Acta Med. Scand., **122**, 175, 1945. (**106.**) **Long, P. H.:** Conn. State Med. J., **7**, 6, 1943. (**107.**) **Longcope, W. T.:** Medicine, **22**, 251, 1943. (**108.**) **Loscalzo, A. E.:** (a) J. Am. Med. Assn., **135**, 496, 1947; (b) J. Nerv. and Ment. Dis., **101**, 537, 1945. (**109.**) **Loveman, A. B.:** J. Am. Med. Assn., **102**, 97, 1934. (**110.**) **Loveman, A.,** and **Simon, F. A.:** Arch. Derm. and Syph., **40**, 29, 1939. (**111.**) **Lowell, F. C.:** J. Am. Med. Assn., **136**, 665, 1948. (**112.**) **Lowenfish, F. F.:** Arch. Derm. and Syph., **37**, 797, 1938. (**113.**) **Lutterloh, C. H.,** and **Shallenberger, P. L.:** Ibid., **53**, 349, 1946. (**114.**) **Lyons, R. H.,** and **Balberor, H.:** J. Am. Med. Assn., **118**, 955, 1942.

(**115.**) **MacKee, G. M., Herrmann, F., Baer, R. L.,** and **Sulzberger, M. B.:** (a) J. Lab. and Clin. Med., **28**, 1642, 1943; (b) Science, **98**, 66, 1943. (**116.**) **Madden, J. F.:** Arch. Derm. and Syph., **26**, 1065, 1932. (**117.**) **Malmros, H.:** Acta Allergy, **1**, 184, 1948. (**118.**) **Martin,**

G. J., **Fisher, C. V.,** and **Thompson, M. R.**: Arch. Int. Med., **69,** 662, 1942. **(119.) Mayer, R. L.**: Toxicodermien. I. Handbuch der Haut und Geschlechtskrankheiten, J. Jadassohn, IV/2, Berlin, J. Springer, 1933. **(120.) Mayo, C. W.,** and **Schlicke, C. P.**: Proc. Staff Meet. Mayo Clinic, **17,** 87, 1942. **(121.) McGinty, A. P., Lewis, G. T.,** and **Holtzclaw, M. R.**: Georgia Med. Assn., **28,** 54, 1939. **(122.) McGovern, T.,** and **Wright, I.**: J. Am. Med. Assn., **112,** 1687, 1939. **(123.) McGuire, J. A.,** and **Shaffer, B.**: Arch. Derm. and Syph., **52,** 342, 1945. **(124.) Mibelli, V.**: Monatsh. f. prakt. Derm., **26,** 333, 1898. **(125.) More, R. H., McMillan, G. C.,** and **Duff, G. L.**: Am. J. Path., **22,** 703, 1946. **(126.) Morrow, P. A.**: Drug Eruptions. Selected Monographs on Dermatology, p. 354, New Sydenham Society, London, 1893. **(127.) Moss, R. E.,** and **Long, W. E.**: Arch. Derm. and Syph., **46,** 386, 1942. **(128.) Moyer, J. H., Jr.**: New England J. Med., **238,** 469, 1948. **(129.) Myers, G. B.,** and **Vonder Heide, E. C.,** and **Balcerski, M.**: J. Am. Med., Assn., **109,** 1983, 1937.

(130.) Naegeli, O., de Quervain and **Stalder, W.**: (a) Klin. Woch., **9,** 924, 1930. **(131.) Naegeli,** cited by Kleeberg, L.: (a) Toxicodermien, in Jadassohn, J.: Handbuch der Haut und Geschlechtskrankheiten, IV/2, p. 350; Berlin, Julius Springer, 1933, (b) Ibid., Klin. Woch., **6,** 25, 1927. **(132.) Nelson, L. M.**: Bull. U. S. Army Med. Dept., **4,** 725, 1945. **(133.) Newman, B. A.**: J. Am. Med. Assn., **101,** 761, 1933. **(134.) Nisbet, T. W.**: Ibid., **134,** 446, 1947. **(135.) Noojian, R. O.,** and **Callaway, J. L.**: North Carolina Med. J., **3,** 239, 1942.

(136.) Omens, D. V., and **Robbins, J. B.**: Arch. Derm. and Syph., **40,** 633, 1939.

(137.) Park, R. G., and **Platts, W. M.**: Brit. Med. J., **2,** 308, 1942. **(138.) Paxton, B. L.**: Arch. Derm. and Syph., **55,** 256, 1947. **(139.) Pelner, L.**: J. Am. Med. Assn., **113,** 113, 1943. **(140.) Peterman, M. G.**: Ibid., **97,** 703, 1931. **(141.) Peters, R. A., Stocken, L. A.,** and **Thompson, R. H. S.**: Nature, **156,** 616, 1945. **(142.) Peterson, W. F.**: (a) Internatl. Clinics, I, 255, 1942; (b) Ann. Allergy, **4,** 43, 1946. **(143.) Pfaff, R. O.**: Calif. Med., **65,** 153, 1946. **(144.) Philpott, O. S.**: Arch. Derm. and Syph., **55,** 525, 1947. **(145.) Pillsbury, D. M.**: Ibid., **34,** 103, 1936. **(146.) Poole, A. K.,** and **Wehger, R. T.**: J. Am. Med. Assn., **102,** 745, 1934. **(147.) Prickman, L. E.,** and **Buchstein, H. F.**: Ibid., **108,** 445, 1937.

(148.) Randall, R. V., and **Seeler, A. O.**: New England J. Med., **239,** 1004 and 1040, 1948. **(149.) Rattner, H.,** and **Graffin, J.**: Am. Pract., **2,** 754, 1948. **(150.) Rattner, H.,** and **Pace, E. R.**: An Outline of Drug Eruptions (Dermatitis Medicamentosa), privately printed, Am. Acad. Derm. and Syph., December, 1946. **(151.) Ray, H. H.,** and **Cunningham, J. S.**: Am. J. Dis. Child., **39,** 1205, 1930. **(152.) Rich, A. R.**: (a) Bull. Johns Hopkins Hosp., **71,** 375, 1942; (b) Ibid, **77,** 43, 1945. **(153.) Ritchie, E. B.,** and **Kolb, W.**: Arch. Derm. and Syph., **46,** 856, 1942. **(153a.) Rives, H. F., Ward, B. B.,** and **Hicks, M. L.**: J. Am. Med. Assn., **140,** 1022, 1949. **(154.) Robinson, H. M.**: South Med. J., **29,** 411, 1936. **(155.) Rosenthal, S. R.**: (a) J. Immunol, **34,** 25, 1938; (b) Am. J. Path., **22,** 473, 1946. **(156.) Rowe, A. H.**: Clinical Allergy, Philadelphia, Lea & Febiger, 1937. **(157.) Ruskin, D. B.**: J. Am. Med. Assn., **137,** 1031, 1948.

(158.) Sandler, I. L.: Med. Ann. Dist. Columbia, **8,** 255, 1939. **(159.) Scheer, M.,** and **Keil, H.**: J. Am. Med. Assn., **102,** 908, 1934. **(160.) Schmitt, C. L.**: Arch. Derm. and Syph., 59, 16, 1949. **(161.) Schwentker, F. F.,** and **Gelman, S. S.**: Bull. Johns Hopkins Hosp., 61, 136, 1937. **(162.) Seidmann, M.**: Arch. Derm. and Syph., **47,** 654, 1943. **(163.) Selye, H.**: J. Allergy, **17,** 231, 1946. **(164.) Sexton, D. L., Pike, G. M.,** and **Nielson, A.**: J. Am. Med. Assn., **116,** 700, 1941. **(165.) Shaffer, B., Lentz, J. W.,** and **McGuire, J. A.**: Ibid, **123,** 17, 1943. **(166.) Shaffer, B.,** and **Morris, P.**: Pediatrics, **2,** 30, 1948. **(167.) Sherman, W. B.**: Am. J. Med., **3,** 586, 1947. **(168.) Sherman, W. B.**: J. Am. Med. Assn., **140,** 447, 1949. **(169.) Simkins, S.**: Ibid., **108,** 2110, 2193, 1937. **(170.) Singh, I.**: Brit. J. Derm. and Syph., 60, 90, 1948. **(171.) Sonck, C. E.**: Acta dermat. vener., Suppl. 6, **22,** 499, 1941. **(172.) Stokes, J. H.,** and **Beerman, H.**: (a) Am. J. Med. Sci., **201,** 611, 1941; (b) Ibid., **202;** 606, 1941; (c) Ibid., **203,** 608, 1942; (d) Arch. Derm. and Syph., **60,** 261, 1949. **(173.) Stokes, J. H., Beerman, H.,** and **Ingraham, N. R., Jr.**: Modern Clinical Syphilology, 3d ed., Philadelphia, Saunders, 1944. **(174.) Stokes, J. H.,** and **Kulchar, G. V.**: Brit. J. Derm. and Syph., **56,** 134, 1934. (175.) **Straus, D. A.**: New England Med., **239,** 956, 1948. **(176.) Sugar, H. S.,** and **Waddell, W. W.**: Ill. Med. J., **89,** 234, 1946. **(177.) Sulzberger, M. B.**: Dermatologic Allergy, Springfield, Ill., Charles C Thomas, 1940. **(178.) Sulzberger, M. B.,** and **Baer, R. L.**: Year Book of Dermatology and Syphilology, 1945, Chicago, Year Book Publishers, 1946. **(179.) Sutliff, W. D., Helpern, M., Griffin, G.,** and **Brown, H.**: J. Am. Med. Assn., **121,** 307, 1943. **(180.) Sutton, R. L.**: (a) Kansas Med. Soc., **38,** 385, 1938; (b) South Med. J., **34,** 1071, 1941.

(181.) **Tate, B. C.,** and **Klorfajn, I.**: (a) Lancet, **1,** 39, 1944; (b) Ibid., **2,** 553, 1944. (182.) **Tedder, J. W.**: Arch. Derm. and Syph., **39,** 217, 1939. **(183.) Thomas, C. C.,** and Hardy, M. K.: J. Am. Med. Women's Assn., **3,** 1, 1948. **(184.) Tonnel,** and **Raviart:** Echo

med. du Nord, **1**, 18, 1897. (**185.**) **Turell, and Leifer, W.**: J. Med. Assn., **118**, 977, 1942. (**186.**) **Urbach, E.**: Klin. Woch., **15**, 1208, 1936. (**187.**) **Urbach, E.**, and **Gottlieb, P. M.**: Allergy, 2d ed., New York, Grune & Stratton, 1946. (**188.**) **Urbach, E.**, and **Sidaravicius, B.**: Klin. Woch., **9**, 2095, 1930.

(**189.**) **Van Winkle, W., Jr., Hardy, S. M., Hazel, G. R., Hines, D. C., Newcomer, H. S., Sharp, E. A.**, and **Sisk, W. N.**: J. Am. Med. Assn., **130**, 343, 1946. (**190.**) **Waddell, W. W.**: Illinois Med. J., **89**, 234, 1946. (**191.**) **Walzer, M. G.**: J. Pediat., **21**, 132, 1942. (**192.**) **Watkinson, G.**, and **Hillis, B. R.**: Brit. Med. J., **2**, 609, 1947. (**193.**) **Wedum, A. G.**: J. Infect. Dis., **70**, 173, 1942. (**194.**) **Weiner, K.**: Arch Derm. and Syph., **42**, 23, 1940. (**195.**) **Weinstein, M.** and **Domm, A. H.**: J. Am. Med. Assn., **117**, 607, 1941. (**196.**) **Whitehill R.**: Bull. U. S. Army Med. Dept., **4**, 724, 1945. (**197.**) **Wien, M. S.**, and **Lieberthal, E. P.**: J. Am. Med. Assn., **117**, 850, 1941. (**198.**) **Wile, U. J.**: Arch. Derm. and Syph., **8**, 407, 1923. (**199.**) **Wile, U. J., Wright, C. S.**, and **Smith, N. R.**: Ibid., **6**, 529, 1922. (**200.**) **Wilson, D. J.**: (a) Ibid., **54**, 377, 1946; (b) Nebraska State Med. J., **32**, 308, 1947. (**201.**) **Wise, F.**: (a) Med. Record, **160**, 602, 1947; (b) Cited by Abramowitz and Noum[2]. (**202.**) **Wise, F.**, and **Abramowitz, E. W.**: Arch Derm. and Syph., **5**, 297, 1922. (**203.**) **Wise F.**, and **Sulzberger, M. B.**: (a) Ibid., **27**, 549, 1933; (b) Penna. Med. J., **37**, 973, 1934. (**204.**) **Wohl, M. G.**, and **Robertson, H. F.**: Penna. Med. J., **47**, 802, 1944. (**205.**) **Wohlstein, E.**, and **Schmidt, L.**: Dermat. Woch., **89**, 1766, 1929. (**206.**) **Wright, C. S.**: Am. J. Syph., Gon. and Ven. Dis., **20**, 660, 1936.

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OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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THE MEDICATED EXTERNAL AUDITORY CANAL

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ALTHOUGH it has been variously estimated that otitis externa constitutes from 5 to 40% of all cases encountered in otologic practice in the United States[5]—the wide variation being due to sectional differences in temperature and humidity—renewed interest in infection of the external auditory canal is essentially a by-product of the war years. This situation is the result of the high incidence and widespread distribution of otitis externa among military personnel in humid tropical and subtropical regions. By virtue of its exposed position to the outside world, the external auditory canal is open to invasion by numerous microorganisms; here a moist milieu containing cellular detritus and cerumen often serves as an adequate culture medium for the growth of bacteria and fungi. While the causative agent of otitis externa can be any one of a variety of bacteria and fungi, it is quite probable that the role of the latter, whether as primary or secondary agents of infection, has been exaggerated.

PHYSIOLOGY AND BACTERIOLOGY. The normal human skin harbors an enormous number of bacteria, which ordinarily are harmless. According to Price[12], these may be divided into a resident and a transient population, the former usually remaining fairly stable. However, some influences, particularly heat and moisture, cause considerable changes in the number of bacteria found on normal skin. Sometimes pathogenic bacteria suddenly become members of the resident flora of the skin; they may then be extremely persistent and difficult to dislodge. Once a foothold is gained in skin already diseased, bacteria are responsible, in greater or less degree, for many diseases affecting the human skin.

In the opinion expressed by Pillsbury[11], the problem of the management of bacterial infection of the skin cannot be dismissed simply by a discussion of the diseases produced, the bacteria concerned and the disadvantages of the various antibacterial agents now available, especially since these agents still have certain definite shortcomings. The management of the more difficult and more resistant cutaneous infections can be improved by a better understanding of the manner in which the skin resists and harbors bacteria and of some of the mechanisms by which bacteria produce harmful effects. Several factors apparently play a role in the remarkable protection afforded by the normal human skin against bacterial invasion. These factors, however, are imperfectly understood, and further basic study is necessary.

A factor of considerable importance is the pH of the skin. The surface of

the skin is enveloped by an "acid mantle," which exhibits pronounced defense against bacterial invasion. Determinations of the pH of the skin by a number of investigators reveal the following: 1. The seborrheic areas of the body are more alkaline than other parts of the skin's surface[5]; 2. the alkaline areas are less bactericidal than the rest of the skin, thus being predisposed to cutaneous infection; 3. in most cases of vesicular eczema there is a shift of the pH of the skin toward the alkaline side; 4. the highest degree of alkalinity is present in fissures associated with eczematous processes[22]; and, 5. moisture, maceration, dead horny tissue and relative alkalinity are 4 favorite conditions for the propagation of many forms of fungi. It has been asserted[21]: "The logical conclusion in managing many skin diseases is not to 'alkalinize' but rather to 'acidify'—at least as regards the skin's surface."

Measurement of the pH of the cutaneous surface of the external auditory canal was undertaken by Fabricant and Perlstein[4] in a series of 131 subjects (27 infants, 44 children and 60 adults) with no apparent lesions in their external auditory canals and either with no visible cerumen or with minimal amounts. A specially adapted glass electrode was employed in conjunction with the Coleman electrometer. In the group of adult male subjects, the pH range of the skin of the external auditory canal was found to be from 5.0 to 7.8, while in the group of adult females, the pH range was found to be from 5.0 to 7.6.

In the group of male infants, the pH range was determined to be from 5.6 to 7.6. In the group of female infants the pH ranged from 5.2 to 7.4. Male children, on the other hand, had a pH range from 6.0 to 7.9, whereas female children had a range in pH from 5.7 to 7.9. In general, there was little difference in the pH range of male and female infants. The pH values fell chiefly within the acid range. Among children the tendency for acid pH values was not nearly as distinct as for other groups.

According to Hayes and Hall[7], otogenic infections in the temperate zone are essentially of 2 types: a winter type due to gram-positive organisms, and a summer type due to gramnegative organisms. The primary infective agents in the latter group are Pseudomonas aeruginosa, (B. pyocyaneus), although in external otitis the infection is often mixed, with both grampositive and gramnegative organisms present. With the recent advance in chemotherapy and the use of antibiotics, otologists can demonstrate how they can eliminate the grampositive organisms and yet have the gramnegative ones flourish, their virulence unabated.

A study of Syverton[19], and his associates reveals that the microbiologic flora of the external auditory canal in otitis externa, which in most cases is mixed, differs from the flora of the normal external auditory canal in the same clime by the inclusion of one or more pathogens. The causative agent of otitis externa can be any one of a variety of bacteria and fungi. Among these are Ps. aeruginosa, K. ozaenae, Staph. aureus haemolyticus, Aspergillus, and probably Monilia tropicalis, Actinomyces and Proteus. The role of fungi undoubtedly has been overemphasized in otitis externa, whether as primary or secondary agents of infection. Simon[17] found that in a series of 90 patients with otitis externa in a tropical climate there were only 21% in whom cultures yielded a fungus. In each one of the 90 cases it was possible to obtain a bacterial growth on culture, and it was believed that bacteria are the primary invaders in otitis externa.

OTITIS EXTERNA. The management of otitis externa still remains a complicated matter, first coming frequently to the attention of the dermatologist, then later to the otologist. The numerous therapeutic regimens are clear proof of the ineffectiveness of any single method of treatment. The introduction of a succession of new drugs has repeatedly seemed to solve the problem, but a painstaking study of various medicaments has invariably brought to light shortcomings which often counterbalanced any effectiveness these agents were thought to possess. Nevertheless, a number of medicaments occupy a useful place in the treatment of otitis externa, even though they do not promote consistent healing.

Dibromosalicylaldehyde has been described as being especially effective against gramnegative organisms, including pseudomonas, and also against fungi. In 71 patients with external otitis under Hayes'[7] management, symptoms were relieved within 24 hours; in 30 the infection resolved in 1 week or less, and the remainder required 2 to 4 weeks' treatment. Wells[20] found the use of penicillin and glycerin wicks (500 units of penicillin per cc. of glycerin) satisfactory in relieving 60 individuals with acute otitis externa. Relief came on gradually and occurred within 24 hours in most instances. Senturia[15a] employed penicillin solutions and penicillin-sulfonamide mixtures in the treatment of 32 patients with otitis externa. Penicillin solution applied topically provided unsatisfactory therapeutic results in 10 of 11 cases diagnosed as acute diffuse, chronic eczematoid, or chronic desquamative external otitis. Rapid subsidence of pain and cellulitis and formation of well-localized abscesses occurred within 24 to 48 hours in 6 cases of circumscribed external otitis treated with intramuscular injections of penicillin. While serving in the armed forces in India, Spence[18] treated a number of infected external auditory canals with 5% sulfanilamide ointment and found that pain generally subsided after the first treatment. Itching and all signs of irritation disappeared in nearly all patients when daily treatment was continued for a period of 7 to 12 days. Some patients required 3 to 4 weeks of therapy.

Pulaski and Matthews[13] declare that 5 patients with chronic otitis externa, due to susceptible organisms refractory to other agents, responded favorably to topical application of streptomycin, 5000 units per cc. On the basis of nearly 1000 cases of otitis externa observed in the army, Birrell[3] makes a number of recommendations. After thorough cleansing the meatus of all discharge, lotions are applied on wicks of ribbon gauze or painted on by means of wool-tipped wire probes. In acute edematous conditions he prefers 10% ichthammol in hypertonic sodium chloride solution, and 10% ichthammol in glycerin after 48 hours of treatment until there is no further exudation. At this point, 1% silver nitrate solution or an alcoholic (1%) solution of gentian violet (medicinal) should be used to harden the meatal skin. Goldstein[6] offers an original treatment for otitis externa. A solution is made by dissolving 1 chlorazene (chloramine, U.S.P.) tablet in 1 ounce of tepid water. The otologist flushes the auditory canal with this preparation on alternate days until the ear is dry. When this is achieved the canal is swabbed with metacresylacetate (cresatin) to which is added thymol in a concentration of 1%.

Furacin solution (5-nitro-2-furaldehyde semi-carbazone) has been reported by Anderson and Steele[1] to be effective against most of the organisms that are prominent in otitis externa. The fungicide employed was a

1% solution of thymol in metacresylacetate. Of the cases treated, 84.1% required no more than 3 visits before clinical well-being was established. The remaining patients responded somewhat more slowly, albeit they improved more rapidly than patients treated with other medicaments. McLaurin[10] describes his experiences with "Sulfamylon", a substance derived from benzylamine and differing from sulfanilamide in that a methylene group is inserted between the benzene ring and the 4-amino group. The preparation was found effective in a large number of patients with otitis externa and chronic otitis media. Reardon[14] maintains that "Iso-Par" ointment, which contains benzylamine salts of isoparaffinic acids, proved a specific medicament for otitis externa. It was found effective as fungicide, bactericide, anesthetic and stimulant to rapid healing.

Otomycosis. In 1844 Mayer first described a disease of the external auditory canal caused by a fungus known as otomycosis. Since then there have been many case reports describing symptoms and signs which are exceedingly diverse; the methods of treatment suggested are as numerous as the fungi isolated. It is believed by Wolf[22] that a factor of considerable importance in explaining the chaotic state of knowledge with respect to otomycosis is the failure to recognize that the disease is not an entity but rather a combination of different diseases caused by widely diverse organisms. In this connection, fungi are seldom isolated from the external auditory canal in pure culture but are frequently accompanied by bacteria. There is no certainty as to whether fungi are primary or secondary invaders. Furthermore, the fungi commonly isolated from infected auditory canals are, with few exceptions, not types whose pathogenicity is definitely established. They are, for the most part, common organisms of the soil able to lead a saprophytic existence outside the body and can be isolated readily from dust or air. At least 53 different species of fungi have been reported to cause otomycosis. These belong to the Aspergillaceae, Mucoraceae, Actinomycetaceae, dermatophytes, yeast-like fungi, and a large variety of miscellaneous fungi imperfectae. The Aspergilli reputedly account for about 90% of the reported cases.

Otomycosis is of limited geographic occurrence, most frequent in tropical and subtropical climates. In the United States the reported incidence is greatest in Florida. Age, sex and race exert no significant influence. Water in the external auditory canals favors the growth and multiplication of fungi. Sharp and his associates[16] assert that the fungi associated with otomycosis ordinarily are saprophytes, such as occur on the normal skin. Excessive proliferation in the external auditory canal leads to a plug of thick, pulplike exudate consisting largely of exfoliated epithelium and fungus mycelium. The external auditory canal does not favor fungus multiplication when it is normal, but only when its cutaneous physiology is altered.

Senturia and Wolf[15b] report *in vitro* experiments testing the action of sulfonamides on fungi isolated from cases of otomycosis. Ten strains of fungi were studied; 4 isolated from the auditory canals of patient with symptoms of otomycosis, and 6 from sources other than the ear but known to be capable of causing otomycosis. The effect of various sulfonamides was determined by sprinkling these agents in powder form onto the surface of agar plates immediately after inoculation. Of the sulfonamides tested—sulfathiazole, sulfadiazine, sulfaguanadine and sulfamerazine—only sulfanilamide was effec-

tive in inhibiting growth of the fungi under study. The experiments suggested that application of powdered sulfanilamide should be helpful in otomycosis unless the disease is caused by monila.

In the pre-sulfonamide-antibiotic era, McBurney and Searcy[9] made a study of the most effective solutions against aspergilli. Numerous substances were tried, the most effective being a thymol-cresatin-alcohol solution. Cresatin alone, thymol in alcohol, and tincture of merthiolate were slightly less effective, and 2% salicylic acid in 95% alcohol was considerably less efficient. Their therapy included cleansing the external auditory canal thoroughly of debris, if necessary with hydrogen peroxide, and followed by mopping with a cotton applicator dipped in olive oil. A 2% solution of thymol in cresatin is then applied with a cotton swab. If there is considerable inflammation, drops of thymol, cresatin and olive oil solution may be used.

REFERENCES

(1.) **Anderson, J. R.**, and **Steele, C. H.**: Laryngoscope, **58**, 1279, 1948.
(2.) **Bernstein, E. T.**, and **Herrmann, F.**: New York State Med. J., **42**, 436, 1942. (3.) **Birrell, J. F.**: Brit. Med. J., **2**, 80, 1945.
(4.) **Fabricant, N. D.**, and **Perlstein, M. A.**: Arch. Otolaryng., **49**, 201, 1949.
(5.) **Gill, W. D.**: Ann. Otol., Rhin. and Laryng., **51**, 370, 1942. (6.) **Goldstein, J.**: Arch. Otolaryng., **42**, 146, 1945.
(7.) **Hayes, M. B.**, and **Hall, F. C.**: Arch. Otolaryng., **47**, 289, 1948.
(8.) **Marchionini, A.**, and **Hausknecht, W.**: Klin. Woch., **17**, 663, 1938. (9.) **McBurney, R.**, and **Searcy, H. B.**: Ann. Otol., Rhin. and Laryng., **45**, 988, 1936. (10.) **McLaurin, J. W.**: Laryngoscope, **58**, 1201, 1948.
(11.) **Pillsbury, D. M.**: J. Am. Med. Assn., **132**, 692, 1946. (12.) **Price, P. B.**: J. Infect. Dis., **63**, 301, 1938. (13.) **Pulaski, E. J.**, and **Matthews, C. S.**: Arch. Otolaryng., **45**, 503, 1947.
(14.) **Reardon, W. T.**: Arch. Otolaryng., **45**, 294, 1947.
(15.) (a) **Senturia, B. H.**: Ann. Otol., Rhin. and Laryng., **55**, 90, 1946. (b) **Senturia, B. H.**, and **Wolf, F. T.**: Arch. Otolaryng, **41**, 56, 1945. (16.) **Sharp, W. B., John, M. B.**, and **Robison, J. M.**: Texas State J. Med., **42**, 380, 1946. (17.) **Simon, E.**: Arch. Otolaryng., **42**, 123, 1945. (18.) **Spence, P. S., Jr.**: Ibid., **47**, 336, 1948. (19.) **Syverton, J. T., Hess, W. R.**, and **Krafchuk, J.**: Ibid., **43**, 213, 1946.
(20.) **Wells, J. L.**: Naval Med. Bull., **46**, 102, 1946. (21.) **Wise, F.**, and **Sulzberger, M. B.**: Year Book of Dermatology and Syphilology, p. 553, 1938. (22.) **Wolf, F. T.**: Arch. Otolaryng., **46**, 361, 1947.

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FEW would contest the view that Vesalius' *Fabrica* (1543) and Harvey's *De Motu Cordis* (1628) were the immortal works that initiated modern medicine—*De Motu* the junior by almost a century. Who, then, has not wondered why, in contrast to the many English translations of Harvey, none of the *Fabrica* or of Vesalius' condensation, the *Epitome*, made in the same year, had ever been published? Even the short *Epitome* has hitherto been available to non-Latinists only in a 1543 German and a unique Dutch translation of 1569, and only a few more than 20 copies of the Latin edition are in existence. But what a change have we seen in Vesaliana in the past decade! First, in 1943, Harvey Cushing's sumptuous Bio-Bibliography, and now, after more than 4 centuries, comes the first English translation of the *Epitome* and also the news that the lengthy *Fabrica* is being translated by Professor J. B. deC. Saunders, a leading authority on Vesalius and 16th century anatomical terminology.

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E. K.

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E. K.

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Geriatric Medicine. Edited by EDWARD J. STIEGLITZ, M.D., Attending Internist, Suburban Hospital, Bethesda, Md. 2d ed. Pp. 773; 180 figs. Phila.: W. B. Saunders, 1949. Price, $12.00.

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